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No. 92-102

IN THE
Supreme Court of the United States

October Term, 1992

WILLIAM DAUBERT and JOYCE DAUBERT, INDIVIDUALLY AND AS GUARDIANS AD LITEM FOR JASON DAUBERT, AND ANITA DE YOUNG, INDIVIDUALLY AND AS GUARDIAN AD LITEM FOR ERIC SCHULLER,
Petitioners,

v.

MERRELL DOW PHARMACEUTICALS, INC.,
Respondent.

ON WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS FOR THE NINTH CIRCUIT

JOINT APPENDIX

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December 2, 1992

PETITION FOR CERTIORARI FILED JULY 7, 1992
CERTIORARI GRANTED OCTOBER 13, 19092

BATEMAN & SLADE, INC. BOSTON, MASSACHUSETTS

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13. "Report on the Safety of Bendectin/Diclectin for Use in the Management of Nausea and Vomiting of Pregnancy," dated Aug. 11, 1989 (submitted in support of Merrell Dow's Reply to Affidavits of Pltfs.' Experts Submitted in Opp. to Deft.'s Mot. for Summ. Judg.), filed Oct. 3, 1989 211

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1. Relevant Docket Entries in Consolidated Case No. 90-55397, *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, and *Schuller v. Merrell Dow Pharmaceuticals, Inc.*

Date	Proceedings
9-12-84	*Daubert* Petition for Removal
9-17-84	*Daubert* Answer
12-20-84	*Schuller* Petition for Removal
12-24-84	*Schuller* Answer
2-12-85	*Schuller* transferred to U.S. District Court for the Southern District of Ohio
2-20-85	*Daubert* transferred to U.S. District Court for the Southern District of Ohio
8-16-85	*Daubert* and *Schuller* returned to U.S. District Court for the Southern District of California
8-5-87	Dauberts' Motion to Consolidate *Daubert* and *Schuller* granted as to all phases of liability
10-20-87	Order bifurcating liability and damages issues and barring presence of plaintiff children during trial of the issue of general causation
12-2-88	*Daubert* First Amended Complaint
8-3-89	Defendant's Motion for Summary Judgment on issue of causation
11/1/89	District Court's Memorandum Decision and Order granting summary judgment to Defendant, filed Nov. 1, 1989
12-14-89	*Daubert* and *Schuller* Notices of Appeal (9th Cir. No. 90-55397)
12/20/91	Court of Appeals' decision affirming the District Court, filed Dec. 20, 1991
4/8/92	Court of Appeals' order denying panel rehearing and rehearing en banc, filed Apr. 8, 1992

2. Complaints and answers in *Schuller* and *Daubert* filed May 11, 1984, Sept. 17, 1984, Dec. 24, 1984, and Dec. 2, 1988

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SUPERIOR COURT OF THE STATE OF CALIFORNIA
For the County of San Diego

NO. 521080

MICHAEL SCH[U]LLER, ANITA DE YOUNG, and ANITA DE YOUNG as Guardian ad Litem for ERIC SCH[U]LLER, a Minor,

Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., a Delaware corporation, (successor to RICHARDSON-MERRELL, INC.), and DOES I through XX, inclusive,

Defendants.

COMPLAINT FOR DAMAGES FOR PERSONAL INJURIES

Come now plaintiffs, MICHAEL SCHULLER, ANITA DE YOUNG, and ERIC SCHULLER, by and through his Guardian ad Litem, ANITA DE YOUNG, and for cause of action against the defendants, and each of them, allege:

FIRST CAUSE OF ACTION

I.

The true names and capacities, whether individual, corporate, associate or otherwise, of defendants, DOES I through XX, inclusive, are unknown to plaintiffs, who therefore sue said defendants by such fictitious names. Plaintiffs are informed and believe and thereon allege that each of the defendants herein designated as a DOE is responsible in some manner for the events and happenings herein referred to and caused injuries and damages proximately thereby as hereinafter alleged.

II.

Defendant MERRELL DOW PHARMACEUTICALS, INC. (hereinafter referred to as "MERRELL"), is a Delaware corporation authorized to do and doing business in the County of San Diego, State of California, to that extent necessary for the jurisdiction of this Court.

III.

Defendants DOES I through V, inclusive, and each of them, were authorized to do and doing business in San Diego, California.

IV.

At all times herein mentioned, defendants, and each of them were engaged in the manufacture, testing, producing, vending, introducing into interstate commerce for sale therein, transporting in interstate commerce for sale therein, advertising, selling and recommending for use to the general public a certain product, to wit, the drug Bendectin.

V.

At all times herein mentioned, each of the defendants herein was the agent, servant and employee of each of the remaining defendants, and at all times mentioned herein each was acting within

the time, place and scope of said agency and employment.

VI.

Defendants, and each of them, knew that if said product was not properly and carefully manufactured, designed, tested, maintained, inspected, and assembled, it would, if used by any member of the general public, be likely to cause serious and permanent injury as is hereinafter more fully set forth.

VII.

Defendants, and each of them, negligently and carelessly designed, manufactured, tested, and sold said product so as to cause it to be in a dangerous and defective and deleterious condition and unsafe for the use and purpose for which it was intended when used as recommended; said condition of said product was known to defendants, and each of them, or should have been discovered by them through the exercise of ordinary care and reasonable diligence, but was not disclosed or made known to plaintiffs and at all times herein mentioned, plaintiffs had no knowledge of said condition or of any danger in the use of said product.

VIII.

The product, Bendectin, was prescribed for ANITA DE YOUNG by her physician during the period when she was pregnant with ERIC SCHULLER; thereafter, as the proximate result of said ingestion during pregnancy, plaintiff ERIC SCHULLER was born on December 18, 1980 with the absence of one hand and other birth defects.

IX.

By reason of the defective, dangerous, deleterious, and unsafe condition of said product, while used in a normal and usual fashion, plaintiff ERIC SCHULLER suffered serious and permanent personal injuries as more fully set forth hereinafter.

X.

As a direct and proximate result of the conduct of the defendants, and each of them, plaintiff ERIC SCHULLER was injured in his health, strength and activity, sustaining severe shock and injuries to his nervous system and person, causing plaintiff

mental, physical and nervous pain and suffering, and resulting in his disability, all to his general damage in a sum which will be shown according to proof.

XI.

As a direct and proximate result of the conduct of the defendants and each of them, plaintiffs were compelled to and did incur expenses for medical care, hospitalization, and other incidental expenses and will have to incur additional like expenses in the future, all in amounts presently unknown to them. Plaintiffs therefore ask leave of court either to amend this complaint so as to show the amount of medical expenses, when ascertained, or to prove said amount at the time of trial.

XII.

As a direct and proximate result of the conduct of the defendants, and each of them, plaintiff ERIC SCHULLER was disabled and will be disabled in the future. Plaintiff has therefore lost earnings and may continue to lose earnings in the future, all in amounts presently unknown to him. Plaintiff asks leave of court either to show the amount of his lost earnings, when ascertained, or to prove said amount at the time of trial.

SECOND CAUSE OF ACTION

I.

Plaintiffs hereby incorporate herein each and every allegation contained in plaintiffs' First Cause of Action on file herein as though fully set fort in length.

II.

Defendants, and each of them, were engaged in the manufacture, testing, producing, introducing into interstate commerce for sale therein, transporting in interstate commerce for sale therein, delivering, advertising, selling, assembling, and recommending to the general public the drug Bendectin for use in the County of San Diego, with all knowledge that said product was to be used by the general public; and that defendants, and each of them, represented and warranted said product was fit for the purposes intended.

III.

During the period that plaintiff ANITA DE YOUNG was pregnant with plaintiff ERIC SCHULLER, she relied upon said representations and warranties and had no knowledge of the unsafe quality of said product.

IV.

Said product was not fit for the purpose for which it was intended in that it was so defectively designed, manufactured, tested, produced, delivered and sold that when used by plaintiff ANITA DE YOUNG in the usual and normal manner, it caused the serious and personal injuries to plaintiff ERIC SCHULLER more fully set forth hereinabove.

THIRD CAUSE OF ACTION

I.

Plaintiffs hereby incorporate herein each and every allegation contained in the First and Second Causes of Action on file herein as though set forth at length.

II.

Defendants, and each of them, warranted and represented that said product was of merchantable quality.

III.

Said product was not of merchantable quality in that when used in a normal manner by plaintiff ANTIC DE YOUNG, it caused the serious and permanent personal injuries to plaintiff ERIC SCHULLER more fully set forth hereinabove.

FOURTH CAUSE OF ACTION

I.

Plaintiffs hereby incorporate herein each and every allegation contained in first three Causes of Action on file herein as though fully set forth at length.

II.

Defendants, and each of them, expressly and by advertising, warranted and represented to the general public and to plaintiffs that

said product was reasonably fit for the purpose for which it was intended.

III.

Plaintiffs relied on said warranties and representations.

IV.

Said product was not fit for the purpose for which it was intended and that, when used in a normal and usual manner, it caused the serious personal injuries more fully set forth hereinabove.

FIFTH CAUSE OF ACTION

I.

Plaintiffs hereby incorporate herein each and every allegation contained in the first four Causes of Action on file herein as though fully set forth at length.

II.

Defendants, and each of them, introduced into the stream of commerce in the United States that certain product more fully described hereinabove while it was in a dangerous and defective condition.

III.

As a direct and proximate result of the dangerous and defective condition of the drug Bendectin, plaintiff ERIC SCHULLER was born with the absence of one hand and other birth defects.

IV.

Defendants, and each of them, are strictly liable to plaintiffs because of the dangerous and defective nature of said product.

SIXTH CAUSE OF ACTION

I.

Plaintiffs hereby incorporate herein each and every allegation contained in the first five Causes of Action on file herein as though fully set forth at length.

II.

Said product, the drug Bendectin, was in a dangerous and defective condition when introduced into the stream of commerce by the defendants, and each of them, in that when used in a normal fashion, it could and would cause serious personal injuries to the users thereof.

III.

The above facts were known to the defendants, and each of them, or in the exercise of due care should have been known to the defendants, and each of them, and in this condition, defendants possessed special knowledge of the materials, design and character of said product. At no time did plaintiffs possess any special knowledge and at no time were they aware that said product was dangerous and defective as aforesaid.

IV.

Although possessed of special knowledge of the dangerous and defective condition and the dangerous propensities of said product, defendants, and each of them, negligently and carelessly failed to warn the plaintiffs of the dangerous and defective condition of said product.

WHEREFORE, plaintiffs pray judgment against the defendants, and each of them, as follows:

For the First, Second, Third, Fourth, Fifth and Sixth Causes of Action:

1. For general damages as proven at the time of trial;
2. For special damages as proven at the time of trial;
3. For lost wages;
4. For costs of suit; and
5. For such other and further relief as the Court may deem proper.

DATED: May 11, 1984 CASEY, GERRY, CASEY, WESTBROOK, REED & HUGHES
By: /s/
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UNITED STATES DISTRICT COURT
For the Southern District of California

NO. 84-2929-K(M)

MICHAEL SCH[U]LLER, ANITA DE YOUNG, and ANITA DE YOUNG as Guardian ad Litem for ERIC SCH[U]LLER, a Minor,

Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., a Delaware corporation, (successor to RICHARDSON-MERRELL, INC.), and DOES I through XX, inclusive,

Defendants.

COMPLAINT FOR DAMAGES

ANSWER OF DEFENDANT MERRELL DOW PHARMACEUTICALS INC. TO COMPLAINT

Defendant Merrell Dow Pharmaceuticals Inc., a corporation, answers the complaint for damages for personal injuries, and admits, denies and alleges as follows:

FIRST DEFENSE
(FIRST CAUSE OF ACTION)

1. Defendant Merrell Dow Pharmaceuticals Inc. (hereinafter Merrell Dow) states that it is without knowledge

or information sufficient to form a belief as to the truth of the allegations contained in Paragraph I.

2. Defendant denies each and every allegation contained in paragraph II, except to admit that defendant Merrell Dow is a corporation doing business in the State of California.

3. Defendant states that it is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in paragraph III.

4. Defendant denies each and every allegation contained in paragraph IV, except to admit that defendant manufactured, distributed and marketed the pharmaceutical product, Bendectin.

5. Defendant denies each and every allegation contained in paragraph V.

6. Defendant denies each and every allegation continued in paragraph VI.

7. Defendant denies each and every allegation contained in paragraph VII.

8. Defendant denies each and every allegation contained in paragraph VIII, except to state that it is without knowledge or information sufficient to form a belief as to the truth of the allegation that Bendectin was prescribed for plaintiff-mother by her physician during her pregnancy with plaintiff Eric Schuller.

9. Defendant denies each and every allegation contained in paragraph IX.

10. Defendant denies each and every allegation contained in paragraph X.

11. Defendant denies each and every allegation contained in paragraph XI.

12. Defendant denies each and every allegation contained in paragraph XII.

SECOND DEFENSE
(SECOND CAUSE OF ACTION)

13. Defendant Merrell Dow incorporates herein its responses to the First Cause of Action hereinabove as though set forth in full.

14. Defendant denies each and every allegation contained in paragraph II, except to admit that defendant manufactured,

distributed and marketed the pharmaceutical product, Bendectin.

15. Defendant denies each and every allegation contained in paragraph III, except to state that it is without knowledge or information sufficient to form a belief as to the truth of the allegations concerning what plaintiff-mother relied upon and her knowledge concerning Bendectin.

16. Defendant denies each and every allegation contained in paragraph IV.

THIRD DEFENSE
(THIRD CAUSE OF ACTION)

17. Defendant Merrell Dow incorporates herein its responses to the First and Second Causes of Action hereinabove as though set forth in full.

18. Defendant denies each and every allegation contained in paragraph II.

19. Defendant denies each and every allegation contained in paragraph III.

FOURTH DEFENSE
(FOURTH CAUSE OF ACTION)

20. Defendant Merrell Dow incorporates herein its responses to the first three Causes of Action hereinabove as though set forth in full.

21. Defendant denies each and every allegation contained in paragraph II.

22. Defendant denies each and every allegation contained in paragraph III, except to state that it is without knowledge or information sufficient to form a belief as to the truth of the allegations concerning what plaintiffs relied upon.

23. Defendant denies each and every allegation contained in paragraph IV.

FIFTH DEFENSE
(FIFTH CAUSE OF ACTION)

24. Defendant Merrell Dow incorporates herein its responses to the first four Causes of Action hereinabove as though set forth in full.

25. Defendant denies each and every allegation contained in paragraph II.

26. Defendant denies each and every allegation contained in paragraph III.

27. Defendant denies each and every allegation contained in paragraph IV.

SIXTH DEFENSE
(SIXTH CAUSE OF ACTION)

28. Defendant Merrell Dow incorporates herein its responses to the first five Causes of Action hereinabove as though set forth in full.

29. Defendant denies each and every allegation contained in paragraph II.

30. Defendant denies each and every allegation contained in paragraph III, except to state that it is without knowledge or information sufficient to form a belief as to the truth of the allegations concerning plaintiff's knowledge.

31. Defendant denies each and every allegation contained in paragraph IV.

FIRST AFFIRMATIVE DEFENSE

1. Plaintiffs' complaint and each claim contained therein fails to state a claim upon which relief can be granted.

SECOND AFFIRMATIVE DEFENSE

2. Plaintiffs' complaint and each claim contained therein is barred by the provisions of the applicable statutes of limitations.

THIRD AFFIRMATIVE DEFENSE

3. Alleges that the plaintiff-mother was fully informed of the risks, if any, involved in the taking of the pharmaceutical product set forth in plaintiffs' complaint and that the plaintiff-mother voluntarily consented thereto, thereby assuming all of the said risks, and thereby becoming the sole proximate cause of any injury, damage or loss to the plaintiffs.

FOURTH AFFIRMATIVE DEFENSE

4. Alleges that if the plaintiffs were injured in any way as a result of any act or omission of defendant, that such was caused and contributed to by their own negligence under the circumstances then existing, and the disabilities, if any which they suffered were likewise so caused and contributed to by their failure to follow the advice and direction of their physicians, nurses and other health care providers and their unreasonable refusal to have medical care and attention and their failure to use ordinary care.

FIFTH AFFIRMATIVE DEFENSE

5. Alleges that if the plaintiffs were injured in any way as a result of any act or omission of the defendant, then such was caused and contributed to by the plaintiff-mother's carelessness, negligence and willfulness under the circumstances then existing and the disabilities, if any, which the plaintiffs suffered, were likewise so caused and contributed to by plaintiff-mother's failure to follow the advice, instructions and directions of her physicians, nurses and other health care providers and her unreasonable refusal to have medical care and attention and by plaintiff-mother's failure to use ordinary care.

SIXTH AFFIRMATIVE DEFENSE

6. Alleges that if it is found that this defendant was negligent or otherwise at fault, which this answering defendant denies, then the conduct, negligence or fault of the plaintiffs or other parties to this action and other persons or entities unknown, must be compared to determine a degree of fault, if any, among said parties and the damages sustained by the plaintiffs, if any, must be reduced and apportioned in relationship to the degree of fault, if any, among the parties.

SEVENTH AFFIRMATIVE DEFENSE

7. Alleges that the injuries in question and damages in question, if any, were the result of the misuse of the product in question. Defendant further alleges that if plaintiffs suffered injuries attributable to the use of any pharmaceutical product

manufactured by this defendant, which allegations are expressly denied, then the injuries, if any, were solely caused and attributable to the unreasonable, unforeseeable and improper use of said pharmaceutical product by plaintiff-mother.

EIGHT AFFIRMATIVE DEFENSE

8. Alleges that the product in question was used after knowledge of the defect, if any, that existed therein.

NINTH AFFIRMATIVE DEFENSE

9. Alleges that any injury, damage or loss allegedly suffered by the plaintiffs was proximately caused by plaintiff-mother's failure to use reasonable means to prevent aggravation of the plaintiff's condition and plaintiff-mother's failure to use reasonable means to mitigate damages, if any, to the plaintiffs.

TENTH AFFIRMATIVE DEFENSE

10. Alleges that the conduct of the plaintiffs, or the conduct of other entities and individuals other than this defendant, whether or not parties herein, proximately caused or contributed to the plaintiffs' alleged injuries and damages. Said conduct comparatively caused or contributed to plaintiffs' alleged injuries and damages. Should it be found that this answering defendant is negligent, which this answering defendant expressly denies, said conduct should comparatively reduce the percentage of any negligence attributable to this defendant.

ELEVENTH AFFIRMATIVE DEFENSE

11. Alleges that all claims are barred in whole or in part by the provisions of the California Commercial Code, section 2725.

TWELFTH AFFIRMATIVE DEFENSE

12. Alleges that plaintiffs' claims are barred by reason of the doctrine of laches and by the fundamental unfairness and prejudice of the excessive and lengthy delay from the date of the alleged ingestion of the pharmaceutical product to the filing of the complaint.

THIRTEENTH AFFIRMATIVE DEFENSE

13. Alleges that the complaint and each claim therein, is barred in that the plaintiffs lack standing to sue this defendant on the claims alleged therein.

FOURTEENTH AFFIRMATIVE DEFENSE

14. Alleges that the manufacture, distribution and sale of the pharmaceutical product referred to in plaintiffs' complaint was at all times in compliance with the Federal Food, Drug and Cosmetic Act.

FIFTEENTH AFFIRMATIVE DEFENSE

15. Alleges that no action or omission of this defendant was a substantial factor in bringing about the alleged injuries of the plaintiffs, nor was any act or omission a contributing cause thereof and any alleged acts or omissions of this defendant were superseded by the acts or omissions of others, including plaintiffs, which were the independent, intervening and proximate cause of any injury, damages or loss sustained by the plaintiffs.

SIXTEENTH AFFIRMATIVE DEFENSE

16. Alleges that, at or about the time, date and place mentioned in the complaint that if any risk was attendant upon plaintiffs' activities which defendant denies, the plaintiffs full well knew of such risks, and voluntarily, and without compulsion or coercion, encountered such risks.

SEVENTEENTH AFFIRMATIVE DEFENSE

17. Alleges that all claims are barred in whole or in part by the applicable statute of limitations (California Code of Civil Procedure, section 340(3).)

EIGHTEENTH AFFIRMATIVE DEFENSE

18. Alleges that all claims are barred in whole or in part by the applicable statute of limitations (California Code of Civil Procedure, section 340.5.)

NINETEENTH AFFIRMATIVE DEFENSE

19. Alleges that all claims are barred in whole or in part by the applicable statute of limitations (California Code of Civil Procedure, section 339(1).)

TWENTIETH AFFIRMATIVE DEFENSE

20. Alleges that all claims are barred in whole or in part by the applicable statute of limitations (California Code of Civil Procedure, section 337(1).)

TWENTY-FIRST AFFIRMATIVE DEFENSE

21. Alleges that all claims are barred in whole or in part by the applicable statute of limitations (California Code of Civil Procedure, section 338(1).)

WHEREFORE, this defendant prays that plaintiffs take nothing by their claims, for defendant's costs of suit, and for such other and further relief as the court deems proper.

DATED: December 21, 1984. HAIGHT, DICKSON, BROWN & BONESTEEL
JEFFERY J. CARLSON
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By: /s/
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UNITED STATES DISTRICT COURT
For the Southern District of California

NO. 84-2013-G(I)

WILLIAM DAUBERT; JOYCE DAUBERT, individually and as Guardians Ad Litem for JASON DAUBERT, a minor,
Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES 1 through 50 inclusive,
Defendants.

FIRST AMENDED COMPLAINT FOR DAMAGES (NEGLIGENCE, STRICT LIABILITY AND BREACH OF WARRANTY)

NO. 84-2929-G(I)

MICHAEL SCHULLER, ANITA DE YOUNG, and ANITA DE YOUNG as Guardian Ad Litem for ERIC SCHULLER,

Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES I through XX., inclusive

Defendants.

FIRST CAUSE OF ACTION
(Strict Liability)

1. At the time of the events complained of herein, plaintiffs William Daubert and Joyce Daubert were residents of the City of Chagrin Falls, State of Ohio. They are the natural parents of Jason Daubert and have been appointed Guardians Ad Litem for purposes of this litigation by order of this Court.

2. Plaintiff Jason Daubert is a minor and was born in and is a resident of the County of San Diego, California.

3. Plaintiffs are informed and believe that defendant Merrell Dow Pharmaceuticals, Inc., is an Ohio corporation, licensed to do business and doing business in the State of California. Defendant Merrell Dow Pharmaceuticals, Inc. (hereinafter "Merrell Dow") was at all times herein mentioned engaged in the business of designing, testing, studying, developing, manufacturing, producing, advertising, selling and distributing drugs and pharmaceutical products, and specifically a drug named Bendectin for sale to and use by members of the general public.

4. The true names and capacities of defendants named herein as DOES 1 through 50, inclusive, are unknown to plaintiffs, who therefore sue said defendants, and each of them, by such fictitious names. Plaintiffs will amend this Complaint to show the true names and capacities when they have been ascertained. Plaintiffs are informed and believe, and thereon allege, that each of the said fictitiously named defendants is responsible in some manner for the

occurrences hereinafter alleged, and that plaintiffs' injuries as herein alleged were proximately caused by said actions.

5. Defendant intended that the drug Bendectin, which was designed, developed, produced, sold and distributed by them, be advertised, sold and/or distributed without warnings as a safe method of controlling nausea and illness during pregnancy.

6. At all times herein mentioned, the defendant knew and intended that Bendectin would be distributed to, purchased by and consumed by members of the general public without inspection for defects and without testing.

7. In or about December 1972 and January of 1983, plaintiff Joyce Daubert was prescribed the drug Bendectin by her physician. She purchased and consumed the drug in accordance with the physician's instructions.

8. Jason Daubert was born on July 26, 1973 with serious and disabling birth deformities and abnormalities. The plaintiffs were not aware that Bendectin was the cause of those abnormalities and deformities until, in late August or early September of 1983, after reading of a June, 1983 jury verdict finding that the product caused birth defects of the same kind suffered by Jason, and after reading in June of 1983 that the product was removed from the market, Joyce Daubert obtained the medical records of the physician who had treated her during her pregnancy and learned that she had been given Bendectin.

9. At the time that she purchased and consumed Bendectin, it was defective and unsafe for its intended purpose in that it failed to warn of the possibility of deformation of the child being carried during the pregnancy, and it was defective in that it caused deformations in children whose mothers consumed the drug during pregnancy.

10. As a proximate result of the conduct of the defendant, plaintiff Jason Daubert was born with permanent deformities and abnormalities. Those deformities and abnormalities have caused Jason and his family, including his mother Joyce, and father William, who observed his birth in the deformed condition, severe emotional distress, all to their general damage.

11. As a further proximate result of the conduct of the defendant, plaintiffs William and Joyce Daubert have incurred, and will continue to incur, medical and related expenses, all to their

special damage. Plaintiff Jason Daubert will incur medical expenses for the remainder of his natural life, all to his special damage according to proof at the time of trial.

12. As a further result of the conduct of the defendants, plaintiff Jason Daubert has suffered great mental and physical pain and suffering and permanent disability, all to his general damage according to proof at the time of trial.

13. As a further proximate result of the conduct of the defendant, plaintiff Jason Daubert has suffered loss of occupational choices and a loss of future earning capacity, all to his general and special damage according to proof at the time of trial.

14. As a further result of the conduct of the defendant, plaintiffs William Daubert and Joyce Daubert were prevented from attending to and will be prevented in the future from attending to their usual occupations while caring for, treating, and arranging for the treatment of plaintiff Jason Daubert, thereby losing past and future earnings, all to their special damage in an amount according to proof at the time of trial.

15. Plaintiffs are informed and believe and upon such information and belief allege that defendant failed to properly design, develop, prepare, produce, test, manufacture and market Bendectin maliciously and in conscious disregard of the safety of the consuming public. Defendant had notice of the relationship between Bendectin and birth defects as early as 1962. Over the next 20 years defendant received reports from independent researchers, the FDA, and their own research staff linking Bendectin to birth defects; specifically limb-reduction defects like that suffered by Jason Daubert. In November, 1962 defendant received a report from the FDA linking Bendectin and limb-reduction defects. Defendant's teratological studies conducted in 1963 confirmed a significant relationship between Bendectin and birth defects and acknowledged the need for more research; defendant failed to conduct any additional animal studies. By 1972, defendant received notice of ninety-six (96) cases of congenital malformations occurring in association with Bendectin usage.

Knowing of the link between Bendectin and birth defects, defendant failed to take the necessary steps to properly prepare, test and market their product. Defendant conducted unscientific and biased studies that misrepresented the safety of Bendectin to the

medical profession and the public. Defendant also withheld information from the FDA that supported the relationship between Bendectin and birth defects.

In addition, defendant marketed, advertised and sold Bendectin without warnings in conscious disregard of the safety of the consuming public and the children whose mothers would ingest the drug during pregnancy. Defendant had notice of the dangerous nature of their drug. Defendant failed to warn of the known or reasonably knowable side effects associated with Bendectin. The relationship between Bendectin and birth defects was willfully, wrongfully and maliciously withheld from the medical profession and the public in conscious disregard of the safety of those who used Bendectin.

Plaintiffs seek punitive or exemplary damages as a result of defendant's conduct, in an amount sufficient to punish or set an example of defendant.

SECOND CAUSE OF ACTION
(Breach of Warranty)

1. Plaintiffs incorporate herein by reference paragraphs 1 through 8 and 10 through 15, inclusive, of the First Cause of Action as though set forth in full herein.

2. Defendant impliedly warranted to Joyce Daubert, as an intended user, that Bendectin would be fit for its intended purpose without warnings as to the potential dangerous consequences of consumption of the drug. Defendant breached that implied warranty by failing to make the drug safe and by failing to warn of the dangerous potentials of its consumption.

THIRD CAUSE OF ACTION
(Negligence)

1. Plaintiffs incorporate herein by reference paragraphs 1 through 8 and 10 through 15, inclusive, of the First Cause of Action as though set forth in full herein.

2. Defendant had a duty to thoroughly research, test and examine the drug which it manufactured before manufacturing it, and had a duty to safely design, develop, prepare, produce, manufacture, and distribute the drug it made, and defendant had a duty to adequately warn of the dangers associated with consuming

the drug, before or at the time of marketing the drug.

3. Defendant breached all of the aforesaid duties by failing to thoroughly research and examine the drug it manufactured before manufacturing it, and by failing to safely design, develop, produce, manufacture and distribute the drug it made, and by failing to warn of the possible dangerous consequences of ingestion of the drug.

WHEREFORE, plaintiffs pray for judgment against defendant as follows:

1. For general damages according to proof;
2. For medical and related and incidental expenses according to proof;
3. For loss of earnings and earning capacity according to proof;
4. For punitive damages in an amount sufficient to punish or set an example of defendant for its failure to properly prepare and market Bendectin, and its failure to warn the medical profession or consuming public of the known or reasonably knowable side effects associated with the drug, in conscious disregard of the safety of the children whose mothers used Bendectin;
5. For cost of suit;
6. For pre-judgment interest; and
7. For such other and further relief as the Court may deem just and proper.

LUCE, FORWARD, HAMILTON & SCRIPPS

By:_____/s/_____
Mary F. Gillick, Attorneys for Plaintiffs WILLIAM and JOYCE DAUBERT, Individually, and as Guardian Ad Litem for JASON DAUBERT

[Declaration of service omitted]

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Attorneys for Defendant,
MERRELL DOW PHARMACEUTICALS INC.

UNITED STATES DISTRICT COURT
For the Southern District of California

NO. 84-2013-G(I)

WILLIAM DAUBERT and JOYCE DAUBERT, Individually and as Guardians ad Litem for JASON DAUBERT and JESSICA DAUBERT, minors,

Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., DOW CHEMICAL COMPANY and DOES 1 through 50 inclusive,

Defendants.

ANSWER OF DEFENDANT MERRELL DOW PHARMACEUTICALS INC. TO COMPLAINT; DEMAND FOR JURY TRIAL

Defendant Merrell Dow Pharmaceuticals Inc. ("Merrell Dow"), answers the plaintiffs' unverified complaint (hereinafter "complaint") as follows:

FIRST DEFENSE
(FIRST CAUSE OF ACTION)

1. Defendant Merrell Dow is without sufficient knowledge or information to form a belief as to the truth of the allegations of paragraph 1.

2. Defendant Merrell Dow is without sufficient knowledge or information to form a belief as to the truth of the allegations of paragraph 2.

3. Defendant Merrell Dow denies each and every allegation of paragraph 3 except to admit that it has its principal place of business in the state of Ohio, that it is licensed to do business and is doing business in the state of California, and that it was engaged in the manufacture and distribution of the prescription product Bendectin.

4. Defendant Merrell Dow is without sufficient knowledge or information to form a belief as to the truth of the allegations of paragraph 4.

5. Defendant Merrell Dow denies each and every allegation of paragraph 5, except to admit that it was engaged in the production and distribution of Bendectin which was sold as a prescription drug for the purposes of treating nausea during pregnancy.

6. Defendant Merrell Dow denies each and every allegation of paragraph 6.

7. Defendant Merrell Dow is without sufficient knowledge or information to form a belief as to the truth of the allegations of paragraph 7.

8. Defendant Merrell Dow denies that Bendectin was the cause of any birth defects allegedly suffered. As to the other allegations of this paragraph, defendant Merrell Dow is without sufficient knowledge or information to form a belief as to the truth of the allegations of paragraph 8.

9. Defendant Merrell Dow denies each and every allegation of paragraph 9.

10. Defendant Merrell Dow denies each and every allegation of paragraph 10.

11. Defendant Merrell Dow denies each and every allegation of paragraph 11.

12. Defendant Merrell Dow denies each and every allegation of paragraph 12.

13. Defendant Merrell Dow denies each and every allegation of paragraph 13.

14. Defendant Merrell Dow denies each and every allegation of paragraph 14.

15. Defendant Merrell Dow denies each and every allegation of paragraph 15.

SECOND DEFENSE
(SECOND CAUSE OF ACTION)

1. Defendant Merrell Dow incorporates by reference its prior responses to the allegations, contained in paragraphs 1-15 of the first defense above as though fully set forth herein.

2. Defendant Merrell Dow denies each and every allegation of paragraph 2.

THIRD DEFENSE
(THIRD CAUSE OF ACTION)

1. Defendant Merrell Dow incorporates by reference its prior responses to the allegations of the complaint, contained in paragraphs 1-15 of the first defense above, and 1 and 2 of the second defense as though fully set forth herein.

2. Defendant Merrell Dow denies each and every allegation of paragraph 2 except to state that Defendant Merrell Dow met all of its legal duties.

3. Defendant Merrell Dow denies each and every allegation of paragraph 3.

FIRST SEPARATE AND AFFIRMATIVE DEFENSE

1. At or about the time, date and place mentioned in the Complaint that if any risk was attendant upon Plaintiffs' activities, which Defendant denies, the Plaintiffs full well knew of such risks, and voluntarily, and without compulsion or coercion encountered such risk.

SECOND SEPARATE AND AFFIRMATIVE DEFENSE

2. The Plaintiff-mother and Plaintiff-father were fully informed of the risk, if any, involved in taking of the

pharmaceutical product set forth in Plaintiffs' Complaint and the Plaintiff-mother and Plaintiff-father voluntarily consented thereto, thereby assuming all of said risk, and thereby becoming the sole proximate cause of any injury, damage or loss to the Plaintiffs.

THIRD SEPARATE AND AFFIRMATIVE DEFENSE

3. If the Plaintiffs were injured in any way as a result of any act or omission of Defendant, then such was caused and contributed to by their own negligence under the circumstances then existing, and the disabilities, if any, which they suffered were likewise so caused and contributed to by their failure to follow the advice and direction of their physicians, nurses and other health care providers and their unreasonable refusal to have medical care and attention and their failure to use ordinary care.

FOURTH SEPARATE AND AFFIRMATIVE DEFENSE

4. If the Plaintiffs were injured in any way as a result of any act or omission of Defendant, then such was caused and contributed to by Plaintiffs' carelessness, negligence and willfulness under the circumstances then existing and the disabilities, if any, which the Plaintiffs suffered, were likewise so caused and contributed to by Plaintiffs' failure to follow the advice, instructions and directions of their physicians, nurses and other health care providers and their unreasonable refusal to have medical care and attention and by Plaintiffs' failure to use ordinary care.

FIFTH SEPARATE AND AFFIRMATIVE DEFENSE

5. If it is found that this Defendant was negligent or otherwise at fault, which this answering Defendant denies, then the conduct, negligence or fault of the Plaintiffs, other parties to this Action and other persons or entities unknown, must be compared to determine the degree of fault, if any, among said parties, and the damages sustained by the Plaintiffs must be reduced and apportioned in relationship to the degree of fault, if any, among the parties, and other person and entities unknown.

SIXTH SEPARATE AND AFFIRMATIVE DEFENSE

6. The injuries in question and damages in question were the result of the misuse of the product in question. Defendant further

alleges that if Plaintiffs suffered injuries attributable to the use of any pharmaceutical product distributed by this Defendant, which allegations are expressly denied, then the injuries, if any, were solely caused and attributable to the unreasonable, unforeseeable and improper use of said pharmaceutical product by Plaintiffs.

SEVENTH SEPARATE AND AFFIRMATIVE DEFENSE

7. The product in question was used after knowledge of the defect, if any, that existed therein.

EIGHTH SEPARATE AND AFFIRMATIVE DEFENSE

8. Any injury, damage or loss allegedly suffered by the Plaintiffs, is proximately caused by Plaintiffs' failure to use reasonable means to prevent aggravation of the Plaintiffs' condition and Plaintiffs' failure to use reasonable means to mitigate damage, if any, to the Plaintiffs.

NINTH SEPARATE AND AFFIRMATIVE DEFENSE

9. All claims are barred in whole or in part by the applicable Statute of Limitations Code of Civil Procedure section 340(3).

TENTH SEPARATE AND AFFIRMATIVE DEFENSE

10. All claims are barred in whole or in part by the applicable Statute of Limitations Code of Civil Procedure section 340.5.]

ELEVENTH SEPARATE AND AFFIRMATIVE DEFENSE

11. All claims are barred in whole or in part by the applicable Statute of Limitations Code of Civil Procedure section 339(1).]

TWELFTH SEPARATE AND AFFIRMATIVE DEFENSE

12. All claims are barred in whole or in part by the applicable Statute of Limitations Code of Civil Procedure section 337(1).]

THIRTEENTH SEPARATE AND AFFIRMATIVE DEFENSE

13. All claims are barred in whole or in part by the applicable Statute of Limitations Code of Civil Procedure section 338(4).]

FOURTEENTH SEPARATE AND AFFIRMATIVE DEFENSE

14. The Complaint is barred by the provisions of Civil Code section 29 in that at the time of the alleged injury, if any, the minor Plaintiff was beginning to develop in the nascent state and the alleged injury occurred prior to or in the course of her birth.

FIFTEENTH SEPARATE AND AFFIRMATIVE DEFENSE

15. All claims are barred in whole or in part by the provisions of California Commercial Code section 2725.

SIXTEENTH SEPARATE AND AFFIRMATIVE DEFENSE

16. The Complaint is barred by reason by the Doctrine of Laches and by the fundamental unfairness and prejudice of the excessive and lengthy delay from the date of the alleged ingestion of the pharmaceutical product to the filing of the Complaint.

SEVENTEENTH SEPARATE AND AFFIRMATIVE DEFENSE

17. The Complaint, and each Cause of Action therein, is barred in that the Plaintiffs lack standing to sue this Defendant on the claims alleged in the Complaint.

EIGHTEENTH SEPARATE AND AFFIRMATIVE DEFENSE

18. The Complaint and each Cause of Action therein, is barred by the provisions of the Code of Civil Procedure, section 389 in that Plaintiffs have failed to join as a party to this action, a party or parties in whose absence complete relief cannot be afforded to the Plaintiffs, to which this Defendant denies the Plaintiffs are entitled.

NINETEENTH SEPARATE AND AFFIRMATIVE DEFENSE

19. The manufacture, distribution and sale of the pharmaceutical product referred to in Plaintiffs' Complaint were in all times in compliance with the Federal Food, Drug and Cosmetic Act.

TWENTIETH SEPARATE AND AFFIRMATIVE DEFENSE

20. Plaintiffs' Complaint, and each purported cause of action set forth therein, is barred by the Doctrine of En Ventre Sa Mere in that the alleged injury occurred prior to the minor Plaintiff's birth while the minor Plaintiff was in utero.

TWENTY-FIRST SEPARATE AND AFFIRMATIVE DEFENSE

21. No action or omission of this Defendant was a substantial factor in bringing about the alleged injuries of the Plaintiffs, nor was any act or omission a contributing cause thereof and any alleged acts or omissions of this Defendant were superseded by the acts or omissions of others, including Plaintiffs, which were the independent, intervening and proximate cause of any injury, damage, or loss sustained by Plaintiffs.

TWENTY-SECOND SEPARATE AND AFFIRMATIVE DEFENSE

22. The Complaint and each Cause of Action contained therein does not state facts sufficient to constitute a cause of action against this answering Defendant.

TWENTY-THIRD SEPARATE AND AFFIRMATIVE DEFENSE

23. The Complaint does not state facts sufficient to constitute a claim for punitive damages.

WHEREFORE, Defendant prays for judgment herein, for Defendant's costs of suit incurred, and for such other and further relief as the court may deem just and proper.

DATED: September 13, 1984

HAIGHT, DICKSON, BROWN & BONESTEEL
JEFFERY J. CARLSON
JOSEPH R. ZAMORA
JOSEPH L. GATTUSO

By: /s/
JOSEPH L. GATTUSO
Attorneys for Defendant
MERRELL DOW PHARMACEUTICALS INC.

DEMAND FOR JURY TRIAL

Defendant Merrell Dow Pharmaceuticals Inc. demands a trial of the above entitled matter by jury, pursuant to Federal Rules of Civil Procedure, section 38.(b).

DATED: September 13, 1984

HAIGHT, DICKSON, BROWN & BONESTEEL
JEFFERY J. CARLSON
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JOSEPH L. GATTUSO

By: /s
JOSEPH L. GATTUSO
Attorneys for Defendant
MERRELL DOW PHARMACEUTICALS INC.

3. Statement of Steven H. Lamm, M.D., D.T.P.H., and curriculum vitae (Ex. A to Deft.'s Mot. for Summ. Judg.), filed Aug. 3, 1989, and excerpts of deposition in *Will v. Richardson-Merrell, Inc.* (Ex. 23 to Pltfs.' Opp. to Summ. Judg.), filed Aug. 22, 1989

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UNITED STATES DISTRICT COURT
For the Southern District of California

NO. 84-2013-G(I)

WILLIAM DAUBERT; JOYCE DAUBERT, individually and as Guardians Ad Litem for JASON DAUBERT, a minor,
Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES 1 through 50 inclusive,
Defendants.

NO. 84-2929-G(I)

MICHAEL SCHULLER, ANITA DE YOUNG, and ANITA DE YOUNG as Guardian Ad Litem for ERIC SCHULLER,
Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES I through XX., inclusive

Defendants.

STATEMENT OF STEVEN H. LAMM, M.D., DTPH

I am a physician and epidemiologist who specializes in assessing the magnitude of risk from exposures to various chemical and biological substances. I am currently the president of Consultants in Epidemiology and Occupational Health, Inc. at 2428 Wisconsin Avenue, N.W., Washington, D.C. 20007. In this capacity, I evaluate the risks of various cancers and birth defects from specific exposures. I have attached hereto my curriculum vitae, which includes a bibliography of various medical articles that I have authored or co-authored.

I first became involved in the Bendectin litigation when asked by the Guardian ad litem for class B plaintiffs, Samuel H. Porter, esq. in the multidistrict litigation in Cincinnati, In Re Richardson-Merrell, Inc. "Bendectin" Product Liability Litigation II, MDL No. 486, to prepare a report for Judge Carl Rubin who had certified a class action in that litigation.

I was sought by the Guardian ad litem to prepare a report for Judge Rubin to assist him in identifying the characteristics of the class. Preparation of this report necessitated assessment of the magnitude of risk of birth defects from maternal ingestion of Bendectin. In order to do this, I reviewed the literature submitted to the court by plaintiffs' and defendant's experts. In the preparation of my preliminary report (October 15, 1984), I reviewed the world's literature on Bendectin and human birth defects, including

all those articles relied upon by either the experts for the plaintiffs or the defendants. These studies included reports on over 130,000 newborn infants. In toto, they showed no difference in the risk of birth defects between those infants whose mothers had taken Bendectin during the first trimester of pregnancy and those infants whose mothers had not.

I next reviewed in a similar manner the literature on Bendectin and limb reduction birth defects. I found no association between Bendectin and the occurrence of limb reduction birth defects.

In addition to reviewing the published scientific literature, I reviewed the overall experience that American women concurrently had with birth defects and with Bendectin usage during the years 1976 to 1984. I found no relationship between the annual frequency of Bendectin usage and the annual occurrences of specific birth defects. As no birth defects showed a drop in frequency when there was a drop in the frequency of Bendectin use, I concluded that there was no evidence from this data that Bendectin usage had anything to do with birth defect rates.

Since the time of that report, I have continued to monitor the literature and data on birth defect rates and on Bendectin usage. My current conclusions are no different from my conclusion of 1984, which is that although approximately 3-4% of all human births exhibit some congenital malformations, the frequency is no greater for the infants of mothers who took Bendectin during the first trimester of pregnancy than for the infants of mothers who did not take Bendectin during the first trimester of pregnancy. Based on my review of the scientific literature, I conclude that maternal use of Bendectin during the first trimester of pregnancy is not a risk factor for human birth defects in general, for limb reduction defects specifically, or for any other particular human birth defect.

I declare under penalty of perjury that the foregoing is true and correct.

/s/
STEVEN H. LAMM, M.D., DTPH

Washington, D.C.

Subscribed and sworn to before me
this 1 day of August 1989.
[notarization omitted]

CURRICULUM VITAE

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Education:

1973-1974 London School of Hygiene and Tropical Medicine
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Diploma in Tropical Public Health (DTPH)

1972-1973 Albert Einstein College of Medicine
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Residency-Pediatrics

1969-1970 Montreal Children's Hospital
Montreal, Quebec, Canada
Residency-Pediatrics
Special Project: Electronmicroscopy of Heart Muscle

1968-1969 University of Oregon Medical School Hospital and Associated Clinics
Internship-Rotating

1964-1968 University of Southern California
School of Medicine
Medical Doctorate (MD)

1963-1964 University of Southern California
Graduate School
Master of Science in Biophysics (MS)
Nerve Action Potential Conduction

1961-1963 University of California, Los Angeles
Bachelor of Science in Chemistry
Radiation Chemistry

1959-1961 Reed College, Portland, Oregon

Employment:

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1980-1981 Chief Executive Officer
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1977-1980 Occupational Physician and Epidemiologist
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1976-1977 Private Practice of Pediatrics
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1974-1976 Senior Epidemiologist
Epidemiology Branch, National Institute of Child Health and Human Development
National Institute of Health
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1972-1975 Lecturer in International Health and Consultant in Family Planning
Development Administrators Training Program
University of Connecticut
Hartford, CT

1971-1973 Medical Director, Middletown Free Clinic
Middletown, CT

1970-1972 Epidemic Intelligence Service Officer from the Center for Disease Control
Atlanta, GA
Attached to the Connecticut State Department of Health, Department of Preventable Diseases and the Connecticut State Tumor Registry

1968 WHO/USPHS Smallpox Eradication Program
Kaduna, Nigeria

Consultant Activities:

1986 Consultant to the Halogenated Organics Subcommittee of Environmental Health Committee of the Science Advisory Board to the Environmental Protection Agency

1986 Senate Commerce Committee on Product Liability Hearing for the Committee on Commerce, Science and Transportation

1986 Department of Health and Human Services, Public Health Service, National Institute of Health on Small Business

1985 Consultant in Epidemiology (Gynecomastia in Haitians), U.S. Department of Justice

1985 Member, Epidemiology Study Section on small business incentive grants to National Institute of Health

1984 Consultant in Drug Effect Epidemiology (Teratology), U.S. Federal Court, Cincinnati, Ohio

1983 Consultant in Epidemiology, Office of Civil Rights, U.S. Department of Justice

1977 Consultant in Birth Defect Epidemiology, National Center for Health Statistics

1973 USAID Consultant in Family Planning Training for Korea, Thailand, Bangladesh, and Pakistan

1972 Vaccine Morbidity Studies in Amazonian Indians, Yale-PAHO

1971 Short-Term Consultant on Cholera to the Phillipines, World Health Organization

Honors:

American Academy of Occupational Medicine, Fellow 1987
American Occupational Medicine Association, Fellow 1985
American College of Toxicology, Associate Member 1984
American College of Preventive Medicine, Fellow 1983
American College of Preventive Medicine
Occupational Medicine 1983
Preventive Medicine 1975

American College of Epidemiology, Charter Fellow 1982
American Academy of Pediatrics, Fellow 1976
American Board of Pediatrics, 1975
Royal Society of Tropical Medicine, Fellow 1974
Annual Prize of the Society for Epidemiologic Research, May 1972

Teaching Experience:

Annual Lectures:
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Committee Assignments:

1988 Chairman, AIDS in the Workplace Symposium, American Industrial Hygiene Conference

1985-Present Chairman, Occupational Medicine Committee
American Industrial Hygiene Association

1984-1985 Chairman, Occupational Epidemiology Committee
American Industrial Hygiene Association

1976-1978 Past Secretary-Treasurer
Society for Epidemiologic Research
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1975 Chairman, Symposia on Bioethics in International Health,
APHA, Chicago, IL

Administrative Experience:

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1974-1976 Senior Epidemiologist
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Editorial Positions:

American Industrial Hygiene Association Journal
American Journal of Public Health
American Journal of Epidemiology
Public Health Reports

Memberships in Professional Societies:

1987-Present American Academy of Occupational Medicine
1987-Present International Commission on Occupational Health
1986-Present American Medical Association
1986-Present International Society of Regulatory Toxicology and Pharmacology
1984-Present Air Pollution Control Association

1984-Present American College of Toxicology
1983-Present American Occupational Medical Association
1983 American College of Preventive Medicine
1983-Present American Conference of Governmental Industrial Hygienists, Inc.
1982-Present American College of Epidemiology
1982-Present American Public Health Association
1980-Present American Industrial Hygiene Association
1976 American Academy of Pediatrics
1974 Royal Society of Tropical Medicine

Publications:

1. "Effects of Bilary Obstruction on Serum Amylase and Lipase Activity," Cucci, Hiyashi and Lamm, Epatologia, 12:829-36, September/October, 1966.
2. "Education Problems in U.S.A.," Lamm, Lancet, 1:839, April 18, 1970.
3. "Control of Salmonella Vector" - Editorial, Lowenstein, Lamm, Gangarosa, J. Infect. Dis., 124:433, October, 1971.
4. "Respiratory Distress Syndrome and Heroin Addiction," Sullivan and Lamm, Lancet, 1:155, January 15, 1972.
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13. "Genetic and/or Environmental Etiologies of Congenital Malformations: An Epidemiological View," Hoffman and Lamm, Am. J. Epidem. 102:456, 1975.
14. "Reactions to Rubella Vaccine and Persistance of Antibody in Virgin-Soil Populations after Vaccination and Wild-Virus-Induced Immunization," Black, Lamm, Emmons, Pinheiro, J. Infect. Dis., 133(4):393-8, April, 1976.
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19. "An Unnecessary Risk to Children," Lamm Brit. Med. J., Sept. 4, 1976, 582.
20. "Reactions to Ruebella Vaccine and Persistence of Antibody in Virgin-Soil Populations After Vaccination and Wild-Virus-Induced Immunization," Lamm, J. Infect. Dis. 133(4):393-398, 1976.
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30. "Upper Respiratory Irritation Symptoms and Formaldehyde Exposure Levels Among Mobile Homes Residents," Lamm, In: Berglund B., Lindvallt, Sundell J. eds. Indoor Air, 3:361-366, 1984.
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Revised 10/4/88

UNITED STATES DISTRICT COURT
For the District of Georgia

No. CV-484-118

DAVID AND BARBARA WILL, et al.,
Plaintiffs,

v.

RICHARDSON-MERRELL, INC.,
Defendants.

Deposition of STEVEN H. LAMM, a witness of lawful age, taken on behalf of the Plaintiffs in the above-entitled cause, pursuant to agreement of counsel, before Harlyne S. Blum, Notary Public, in the law offices of Paulson, Nace & Norwind, 1818 N. Street, N.W., Washington,D.C. 20036, at 1:10 p.m., Friday, December 27. 1985.

APPEARANCES:

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[44]
teratogen in the absence of evidence from the laboratory.

In the same sense -- what I mean by "level of proof," I would say that it was generally accepted that epidemiology has demonstrated that cigarette smoking causes lung cancer. There are certain people who will not accept that totality of that information as so indicated. Nonetheless, I think that the evidence is quite strong, and based on that, one can say that cigarette smoking is quite capable of causing lung cancer.

Q. Would you agree that in some instances of trying to determine whether or not a drug is capable of causing a birth defect, that it would be helpful to utilize epidemiologic studies and other scientific evidence that is available?

A. I'm bothered by the use of "capable."

Q. I know you are. Go ahead. You can answer the question.

A. I forgot the question.

Q. I probably did, too, Doctor.

Q. Would you agree that it would be useful then, in trying to determine whether or not Bendectin is capable of causing a birth defect in humans, to utilize epidemiological evidence as well as other available scientific evidence?

THE WITNESS: Would you read back the question?

[45]
(The pending question was read by the reporter.)

THE WITNESS: Yes.

BY MR. NACE:

Q. Would the other available scientific evidence include animal studies?

A. At times.

Q. Would it at times include knowledge of the structure and activity of a particular component of the drug?

A. It might.

Q. Might it also include knowledge about in vitro studies that were done?

A. I'm not sure what you mean by "in vitro studies," specifically, but it might.

Q. Might it also include information about a drug that

might come from the company's own files as opposed to formal epidemiological studies?

MR. WOODSIDE: Object to the vagueness and general nature of the question. Go ahead.

THE WITNESS: Valid information is always useful.

BY MR. NACE:

4. Excerpts from deposition of John Davis Palmer, Ph.D., M.D., (Ex. C to Deft.'s Mot. for Summ Judg.), filed Aug. 3, 1989

UNITED STATES DISTRICT COURT
Southern District of California

NO. 84-2929-G(I)

MICHAEL SCHULLER, ANITA DE YOUNG, and ANITA DE YOUNG as Guardian Ad Litem for ERIC SCHULLER, a Minor

Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., a Delaware Corporation (successor to RICHARDSON-MERRELL, INC.) and DOES 1 through XX., inclusive

Defendants.

No. 84-2013-G(I)

WILLIAM DAUBERT and JOYCE DAUBERT, individually and as Guardians Ad Litem for JASON DAUBERT and JESSICA DAUBER, Minors,

Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., et al.,

Defendants.

DEPOSITION OF JOHN DAVIS PALMER, M.D.
December 16, 1988, Tucson, Arizona

WOPPERT, HAIGHT, BRUNOTTE & GARCIA
Certified Court Reporters
10 East Broadway, Suite 10
Tucson, Arizona

[15]
may be four months or it may be six. I don't remember for sure.

Q. You mentioned that you had done studies with human beings. Have you ever designed an epidemiology study?

A. No.

Q. Have you ever published an epidemiology study?

A. No.

Q. Have you ever designed an epidemiology study?

A. No.

Q. Who has funded your research over the years?

A. At the University of Minnesota as a graduate student my research was funded by the Sterling Winthrop Pharmaceutical Company and in part by the National Institutes of Health. They supported my salary as a fellow in the combined M.D./Ph.D. program.

At the University of Colorado my research was funded by institutional funds which probably had an origin from the National Institutes of Health, part of an institutional grant that's awarded based on the amount of the support that institution received from the NIH. But that was institutionally administered money,

* * *

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but these two papers and the abstract form the basis of the opinion that I have been able to give you this afternoon.

Q. What published epidemiological studies support your opinion that Bendectin causes limb defects?

A. With respect to humans, I mean, published studies with the studies done with humans or published studies of another

nature, animal studies vis-a-vis the drug may cause limb reduction.

Q. Right now my question is just with respect to the published human epidemiological studies. Which of those support your opinion that Bendectin causes limb defects in humans?

A. I don't believe any of them directly address that issue and find a positive association by the scientific criteria that are used by those authors. Yet, almost all the authors, and in particular the Boston group, make statements in their papers or in subsequent responses to letters to the editor and communications of that type that their analysis of the data and using techniques of the type employed, do not exclude the possibility of an association between the use of Bendectin and a variety of other defects, implied limb defects as well.

MR. NACE: I want to enter an objection. I

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assumed that your question dealt only with whether there were any papers specifically on limb reduction defects that enable limb to form an opinion on the reduction defects, is that what you were asking?

MR. MESSER: That wasn't the question.

THE WITNESS: Then I misunderstood your question.

BY MR. MESSER:

Q. Are there any published epidemiological studies that conclude Bendectin causes limb defects in humans?

A. Not that I know of.

MR. NACE: I am going to object until you define what you mean by the word conclude. You mean beyond a reasonable doubt, sir, or within a reasonable degree of certainty, or do you mean within ninety-five certainty?

I think your question is improper, irrelevant, immaterial and designed to trick the witness.

THE WITNESS: I do not believe the word conclusion is used in the papers. Ordinarily in papers of the type that we're talking about where there is a hypothesis vis-a-vis exposure in the development of a defect, the authors when they find a negative result, in

* * *

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Q. But you have never done a study in the field of teratology, have you?

A. That's correct.

Q. Never published anything in the field of teratology?

A. That's correct.

Q. Have you ever done any study on Bendectin?

A. No.

Q. Have you ever done any study on doxylamine?

A. No.

MR. NACE: I have to object. What are we talking about by "study"? I mean, you may have misled the doctor.

THE WITNESS: I have never published any reports on Bendectin or doxylamine. I have studied the literature.

BY MR. MESSER:

Q. But you have never done any laboratory or clinical-type investigation with Bendectin on doxylamine, have you?

A. That's correct.

Q. Isn't it true, Doctor Palmer, that none of the published epidemiological studies states that Bendectin causes birth defects?

A. No.

* * *

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asked.

Q. What doctors at the University of Arizona consult on birth defect cases with respect to causation?

A. I don't know.

Q. Do you know of any doctors at the university who consult with parents who have had a child with birth defects?

A. I'm sure there are some, but I don't know who they are.

Q. Do you know what field they practice in?
A. No, I could only speculate.
Q. But you are not one of those doctors?

A. I don't deal with the parents of my patients. I do have parents who have birth defects of one type or another and once in a while we discuss those issues with those patients.
Q. Have you given a patient an opinion about the cause of a birth defect?
A. I'm sure I have when it comes to adults with certain types of birth defects, but I don't recall any specific examples.
Q. Have you ever consulted with a patient and advised him that the cause of his birth defect was exposure to a drug?
A. Not to my recollection.
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Q. Have you ever advised a patient that the cause of the birth defect was exposure to any chemical or other environmental agent?
A. Not to my recollection.
Q. Now, are you aware that Bendectin or Debendox, D-e-b-e-n-d-o-x, has been approved for use in Britain?
A. Yes.
Q. Are you aware that the British government has looked into Bendectin and did not find it to be unsafe?
A. No.
Q. Do you disagree with the position taken by the British authorities as to the medical evidence pertaining to Bendectin?
MR. NACE: Objection. Do you want to tell us what the position is? Do you have a document?
THE WITNESS: If it's a position, to-wit: That this drug is safe for administration to gravid females, I disagree with that.
BY MR. MESSER:
Q. And are you aware that the West German government has approved the use of Bendectin?
A. No.
Q. And if they had, would you disagree with

* * *

5. Affidavit of Stuart A. Newman, Ph.D (Dock. No. 184), filed Sept. 28, 1989

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UNITED STATES DISTRICT COURT
Southern District of California

No. 84-2013-G(I)

WILLIAM DAUBERT and JOYCE DAUBERT, Individually and As Guardian Ad Litem for JASON DAUBERT, a Minor,
Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES 1 through 50 Inclusive,
Defendants.

NO. 84-2929-G(I)

MICHAEL SCHULLER, ANITA DE YOUNG, and ANITA DE YOUNG as Guardian ad Litem for ERIC SCHULLER,
Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES 1 through 50., Inclusive
Defendants.

[2] **AFFIDAVIT OF STUART NEWMAN, P[h].D.**

Stuart A. Newman, Ph.D. states as follows:

1. I am a member of the Department of Cell Biology and Anatomy, New York Medical College, Valhalla, New York where my duties include teaching and research. My curriculum vitae is attached. I have particularly been involved in research on the development of the limb, in which area I have concentrated my work for approximately 17 years. I have received several research grants with respect to my work on limbs.

I have received my degree with my major in chemistry from Columbia University and received my Ph.D. from the University of Chicago. During my Ph.D. training I received courses in chemistry, physics, biology and I did original research. I did work on how chemistry explains biological systems and how chemistry relates to how cells work. Specifically my doctoral paper involved the subject of how chemistry can explain how living systems work. I received further training at the Marine Biological Laboratory at Woods Hole, Massachusetts where I studied embryology and received a certificate in embryology from the Marine Biological Laboratory which is one of the foremost research and teaching institutes in the country with respect to the

fields of embryology, physiology and marine biology. I specifically studied embryology which is the study of how embryos develop. (A very small number of people are
[3]
selected to attend the Woods Hole program.)

I have taught numerous chemistry courses and have held all the ranks from instructor to where I am currently a full professor in the Department of Cell Biology and Anatomy, and I have taught histology, cell biology, etc. I also teach laboratory techniques and lecture to medical students. I have been a research fellow at the University of Sussex in England, where I was a visiting fellow in the Department of Biological Sciences and I conducted independent research supported by the British government. I have taught courses in molecular biology and cell development. Molecular biology is basically the study of how cells regulate the synthesis of their various components. Developmental biology is a specialized area that has to do with tissues as they change their shape and their form and change their type, which particularly involves the embryo and how the body is taking form.

I am also a member of the Department of Medicine at the New York Medical College. My current duties include directing the histology courses and directing a laboratory where we do developmental, cell, and molecular biology, specifically including work on the development of the limbs.

I have served as a consultant to the National Institute of Health where I serve on a panel to help determine what funds are awarded for research. I have been a peer reviewer for the National Science Foundation and a consultant to
[4]
several scientific journals and magazines and published articles that result from scientific research. I have specifically been a peer reviewer for Cell, Developmental Biology, Science, Cell Differentiation, Nature, Differentiation, and several others. I have published more than 40 articles myself, many of which involve the limb as the major subject. I have lectured to other doctors with respect to limbs and how they form on more than 70 occasions in the United States and abroad. I have been keynote speaker at the British Society of Developmental Biology Meeting

on the development of the limbs. I have also published approximately 10 chapters in text books, some of which deal with limb development.

I have done in vitro studies which are basically the way scientists now have to look at systems, and parts of the body in isolation from other parts of the body to understand how tissues behave. The in vitro studies that I have done have primarily involved limb tissues. These in vitro studies are generally and reasonably relied upon by developmental biologists to try to determine how the body develops and are the most modern scientific tool on the subject. In vitro studies are also generally used and relied upon to help determine what causes human bodies to not develop the way they would normally develop. I am familiar with antihistamines and how they affect the cells from my scientific background, my reading of the scientific

[5]

literature and general understanding in the field of biology and biological chemistry.

My Ph.D. is in the field of chemical physics. I do research on the causes of birth defects. I am frequently consulted by physicians with respect to sharing my expertise on the cause of birth defects.

My work specifically relates to the area of teratology (which is the study of abnormal development) because if one is trying to understand the mechanisms of normal development, one must also understand the mechanisms of abnormal development.

2. Utilizing the type of data that is generally and reasonably relied upon by scientists who are trying to determine whether a drug is teratogenic, it is my opinion within a reasonable degree of scientific certainty that the antihistaminic component of Bendectin, doxylamine succinate, is a teratogen. That means that it has the capability of affecting the normal development of cells in the human embryo and thereby causing abnormalities. Specifically, it is my opinion within a reasonable degree of scientific certainty that the antihistaminic component of Bendectin, doxylamine succinate, is capable of causing abnormal development of the limb in the human. This includes abnormal (which includes lack of) development of the bones, muscles and other portions of the

limb.

[6]

3. The development of the limb in the human is basically the same as in other animals including chickens, birds, monkeys, rabbits, rats, dogs, etc. The development of the limb involves a process called chondrogenesis which is the formation of cartilage. The entire limb structure is laid out as cartilage and only after that occurs does it begin to change into bone. Part of the process of chondrogenesis is the cell to cell communication that takes place which affects how the cells act and react. This is a chemical process. Both proteoglycan and collagen are important materials in the development of the process of chondrogenesis. Mesenchyme cells have neither cartilage type collagen nor cartilage-type proteoglycan which can be measured. It is only after mesenchyme cells communicate with each other that they begin to make new materials and that you can then detect proteoglycan and collagen. In vitro studies specifically can analyze and measure the development of the foregoing. Proteoglycan is necessary in order to cement cells together - without it, structures of the limb may be missing or improperly formed.

4. A teratogen is a substance that causes abnormal development and chemicals including drugs may be teratogens.

We know that doxylamine succinate, a component of Bendectin is, an antihistamine. Antihistamines have similar characteristics. Specifically there is a strong similarity between doxylamine succinate and the drug Benadryl, another

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antihistamine. Numerous articles have been written concerning the findings of antihistamines on pregnancy. These include articles by Shelesnyak, McKay, King, and others. The findings were that antihistamines may damage the fetus. It is important to scientists in determining how one antihistamine will act to know how others would act, so that knowledge about one antihistamine or a particular class is helpful in understanding other antihistamines of the same or similar classes and it is helpful in determining such actions. The kinds of defects in fetuses that were found with antihistamines include limb defects, cleft palate defects and the like.

5. All of the foregoing articles and data are helpful in determining whether or not a particular antihistamine would be capable of being a teratogen and effecting the development of the body and the limbs in particular and is the type of data that is generally and reasonably relied upon to help determine teratogenicity.

6. Scientific articles and work by Hassell and Horigan; Guntakatta; Budroe; BGA; all deal with in vitro studies concerning doxylamine succinate and Bendectin. In vitro studies are generally and reasonably relied upon to help determine the teratogenicity of a substance and have been used for the purpose of studying how limbs develop and why they develop abnormally or not at all. One of the outstanding articles (Hassell and Horigan) was conducted at

[8]

NIH and shows that Bendectin and doxylamine succinate have the ability to interfere with the growth or differentiation of cells and reduces the amount of proteoglycan available. The technique used by Hassell and Horigan is one that is generally and reasonably utilized for these purposes and is a verified technique.

Guntakatta's results are concordant with Hassell and also shows the effect of Bendectin on DNA. The BGA study shows that Bendectin has the ability to cause chromosomal breakage which is another indication that the substance is toxic or poisonous to the cell. The BGA study shows chromosomal abnormalities in the presence of Bendectin. There is in fact a relationship between the concepts of mutagenicity and teratogenicity in that one would reasonably rely upon both kinds of studies to help determine whether or not a drug is a teratogen because it would tell whether or not the drug is toxic to cells. The Budroe study also shows that the doxylamine succinate component of Bendectin had the ability to damage DNA.

Based on the various in vitro studies that have been performed including the ones identified previously within a reasonable degree of certainty Bendectin and doxylamine succinate, its antihistaminic component, interferes with a number of aspects of the cell. It interferes with the conduction of nerve cells, DNA synthesis, damages DNA to cause unscheduled DNA synthesis, and reduces the amount of

[9]

proteoglycan formed during the process of chondrogenesis. It is in fact therefore toxic to the normal maintenance of properties of cells. This data further shows within a reasonable degree of scientific certainty that doxylamine succinate and Bendectin have the capability of interfering with normal limb development in the human.

7. It is my opinion based upon my education, training, and experience, specifically with respect to my experience with limb development, utilizing the in vitro studies and the pharmacology aspects of Bendectin that are known to me and is known to others including the fact that doxylamine succinate is an antihistamine which is a lipophilic, amphipathic substance that Bendictin is capable of interfering with the development of the limb in the human being and causing birth defects in the developing limb of the human being and that Bendectin is a human teratogen in the normal therapeutic dose.

8. I have further reviewed animal studies including those by Dr. Rolle, by RTI and the company studies and they also are helpful in determining the teratogenicity of Bendectin and in my opinion within a reasonable degree of scientific certainty support the in vitro studies and enable one to conclude that Bendectin (and its component doxylamine succinate) does in fact have the ability of being a teratogen in a human being at normal therapeutic doses.

[10]

9. The type of science that I have been describing thus far is generally laboratory science which is considered a hard science in that its conclusions are not substantiated in the basis of statistical inference as much as upon controlled experiments where individual variables or components are changed only in a very precise fashion as opposed to epidemiology studies (which is known as a "soft science" because of the extreme numbers of variables that are involved). True scientists who deal with the subjects encompassed herein, namely developmental biology would not rely solely upon epidemiological data to draw conclusions about the ability of a chemical, e.g. drug, to affect the cells in the developing human fetus.

Moreover, it is not only proper, but common practice to make inferences about how drugs are going to affect humans and have affected humans based upon pharmacology data, animal studies, and in vitro studies. Such data are all of the type that is generally reasonably relied upon to help determine whether or not a drug is capable of causing an effect in a human being, such as a teratogenic effect. It is this type of data, as described heretofore, along with my education, training, and many years of experience that permits me to conclude that Bendectin and its component doxylamine succinate are teratogenic and thereby capable of adversely affecting the development of cells in the human fetus whereby abnormalities including defects occur.

[11]

Moreover, it is my opinion within a reasonable degree of certainty based on all of the foregoing that Bendectin is in fact teratogenic in the human being at the normal human therapeutic dose.

/s/
Stuart A. Newman, Ph.D.

Sworn to and subscribed in my presence on this 22nd day of September, 1989.

/s/
Notary Public

My commission expires:
1/31/91

[SEAL]

6. Affidavit of Frederick Crescitelli, Ph.D, and curriculum vitae (Dock. No. 183), filed Aug. 22, 1989

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UNITED STATES DISTRICT COURT
For the Southern District of California

NO. 84-2013-G(I)

WILLIAM DAUBERT; JOYCE DAUBERT, individually and as Guardians Ad Litem for JASON DAUBERT, a minor,
Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES 1 through 50 inclusive,
Defendants.

NO. 84-2929-G(I)

MICHAEL SCHULLER, ANITA DE YOUNG, and ANITA DE YOUNG as Guardian Ad Litem for ERIC SCHULLER,
Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES I through XX., inclusive
Defendants.

[2] **AFFIDAVIT OF FREDERICK CRESCITELLI**

Frederick Crescitelli states as follows:

1. I am emeritus professor of biology at the University of California in Los Angeles where I have been a professor since 1949. I have a Ph.D. in biology and bio-chemistry and an honorary medical degree from the University of Linkoping in Sweden. I received my Bachelors Degree in 1930 from Brown University, a Masters Degree in 1932, and a Ph.D. in 1934. I received a Phi Beta Kappa, Sigma Psi and Williams Keene Award University for research work. I was graduated summa cum laude. I have had a National Science Foundation Senior Fellowship and a fellowship to work at Johns Hopkins University.

My profession is as a scientist and biologist, and I have
taught at Brown University, University of Iowa, University of Washington, Stanford University, University of Southern California, University of California, Los Angeles, Johns Hopkins University, University of London, and the University of Cologne in Germany. During all of this time I was teaching but was also involved in research. I am a member of numerous scientific associations, including the Federation of American Biologists, the American Association of Scientists, the American Association for the

Advancement of Science, the American Academy of Neurology, the Biophysical Society, and others. I have served on numerous advisory committees of NIH. My undergraduate training is in biology with accessory
[3]
training in physics and chemistry; my Masters Degree is in biochemistry and my Doctorate Degree is in physiology. All my biologic work has been either biochemical in nature, pharmacological in nature, or physiological in nature, and I have worked with all kinds of animals. The purpose for doing the research in animals is for a greater understanding of the physiology of man. I have approximately 125 formal papers, 80 to 100 short notes or abstracts, and a half-dozen reviews. A copy of my curriculum vitae is attached.

I have authored articles concerning antihistamines and related compounds and their effect on nerve fibers.

I have further specifically performed studies on the substance known as doxylamine succinate, an antihistamine. I have further reviewed the pharmacological data and animal studies, as well as in vitro studies pertaining to Bendectin and doxylamine succinate.

2. It is my opinion, within a reasonable degree of scientific certainty, that based upon my education and training and experience, my own work, and my review of the scientific literature, that Bendectin and doxylamine succinate (its antihistaminic component) is a teratogen. That is, it is a chemical that is capable of affecting the development of cells in the human fetus at normal therapeutic doses.

Moreover, our study shows that doxylamine succinate has the ability to block nerve conduction. More specifically, it is my opinion, based on the, foregoing, that antihistamines,
[4]
within a reasonable degree of scientific certainty, produce irreversible damage to nerve fibers. This includes the antihistaminic substance doxylamine succinate.

It is well accepted in the scientific field that a substance such as doxylamine succinate is capable of reaching the fetus and passing through the placenta. Moreover, doxylamine succinate is an amphipathic substance, which means it orients itself in water - fat layers, and that, specifically, the human embryo during the first

trimester is a complex multi-molecular system with fatty material. Antihistamines, in particular, are known to get into cells rather easily, in part because of their relatively small molecular weight.

3. I must point out that at the cellular and molecular levels the qualitative effects obtained in carefully designed and confirmed experiments will be the same regardless of the organism employed. Whether one uses a human, a monkey, a rabbit, a frog, or a fish, the fundamental responses will be qualitatively the same so the interpretations made from experiments on species A are applicable to species B. There are so many examples of this fundamental truth that the point need not be labored. DNA, for example, is the genetic material for all organisms. ATP is the energy-releasing compound of universal applicability. Nerve conduction is the same process in squid and man. Muscle contraction involves the same molecular reactions in ali vertebrates. The chemical

[5]

transmitters of the nervous system are functional elements in vertebrates and in the few invertebrates that have been investigated. Belief in this dogma - for dogma it is - has led to the advances in biology and medicine that we know today.

The concentration of a drug in the bulk phase of a system of living cells is not necessarily the same as the concentration at or within the cells of that system. Many reagents are preferentially absorbed to cell surfaces so as to achieve local concentrations well above that of the bulk phase. This is especially true of substances having amphipolar structure, i.e., a lipophilic structure at one end and a hydrophilic moiety at the other end. Such is the structure of many antihistamines, including doxylamine.

An important point worth noting is that the very early fetus is quite a different organism than the mother or the late embryo. Neither the liver, with its detoxifying mechanisms, nor the kidneys, with their homeostatic regulating power, are present so that the organism is at the mercy of agents reaching it via the placental circulation, including doxylamine.

4. The two antihistamines that are most closely related structurally, physiologically, and pharmacologically, are Benedryl and doxylamine succinate.

It is my opinion, within a reasonable degree of scientific certainty, therefore, that studies that have been conducted on Benedryl and data obtained from such studies are

[6]

also quite applicable to doxylamine succinate.

5. Based on my education, training, experience, and the studies that I have performed, plus the medical literature and scientific literature, it is my opinion, within a reasonable degree of scientific certainty, that doxylamine succinate is a teratogen in humans; that it interferes with nerve function which is necessary for normal development of muscles and limbs and other structures of the body; and it has the ability to, in fact, effect the development of limbs in the human. Moreover, this is a physiological problem which is the subject of biology, anatomy and pharmacology. This is an area that I have worked with for 30 to 40 years. Moreover, it is my opinion that in the normal therapeutic dose, Bendectin and its compound doxylamine succinate is a teratogen.

6. I have further reviewed the in vitro studies pertaining to Bendectin and they also add to our scientific knowledge of Bendectin and its antihistaminic compound, or doxylamine succinate, and they are also helpful and generally and reasonably relied upon to help determine teragenocity and, in fact, the in vitro studies pertaining to Bendectin and doxylamine succinate do show that Bendectin and doxylamine succinate are teratogenic.

Moreover, animal studies are also helpful and generally and reasonably relied upon to help determine whether or not a drug is teratogenic and capable of affecting the human cells and the animal studies on Bendectin and doxylamine succinate,

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indicate within a reasonable degree of scientific certainty that Bendectin and its component doxylamine succinate are teratogenic in the human.

7. Moreover, it is scientifically improper to rely solely upon epidemiology studies to determine whether or not a drug is a teratogen. One of the primary reasons for that is that epidemiological studies are generally inconclusive because of the subjective nature of the studies and the variables that are involved. No teratogen has been discovered through an epidemiological study and it is absolutely incorrect to assert that they are the best evidence

on the subject. It is further clear that, in fact, they are the least reliable data of all the data available on Bendectin.

8. In summary, it is not epidemiological studies that scientists rely upon to determine whether or not a drug is a teratogen. Much better scientific data includes pharmacology data, animal studies, and in vitro studies. This is the type of data generally and reasonable relied upon to determine if and how a substance is going to have a toxic effect upon a cell and it is the developing cells that determine whether or not the human body will develop normally or abnormally. Using the available scientific data, i.e., the pharmacologic data, the animal data, and the in vitro studies, including my own

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study on antihistamines, it is my opinion, within a reasonable degree of scientific certainty, that doxylamine succinate is a teratogenic substance capable of producing abnormalities in the human fetus, when ingested at normal theraputic doses.

/s/
Frederick Crescitelli

STATE OF CALIFORNIA
COUNTY OF LOS ANGELES

Subscribed and sworn to before me this 26 day of September, 1989

/s/
Notary Public

[Official Seal]

/s/
My Commission Expires

CURRICULUM VITAE

FREDERICK CRESCITELLI

Born:
June 23, 1909, Providence, R.I.

Education:
Brown University, Ph.B. 1930
Brown University, Sc.M. 1932
Brown University, Ph.D. 1934

Honors:
Phi Beta Kappa, 1932
Sigma Xi, 1932
Summa Cum Laude, 1934
Carpenter Premium, 1934
Keen Fellow, Brown University 1934-1935
Mellon Fellow, Johns Hopkins University 1946 (six months)
National Research Science Fellowship 1934
Senior Fellowship, National Science Foundation 1959 - 1960.

Positions:
Colby Junior College 1935-1936
Research Associate, University of Iowa, 1936-1940
Instructor, Department of Physiology, University of Washington, Seattle, 1940-1941
Acting Assistant Professor, Department of Physiology, Stanford University, 1941-1943.
Visiting Assistant Professor, Aviation Medicine, University of Southern California, 1943-1944
Medical Research Center, Edgewood Arsenal, Maryland, 1944-45
Fellow, Wilmer Institute, Johns Hopkins University, 1946
Associate Professor and Professor, University of California, 1946-present

Sabbatical leave to University of Cambridge, England, 1952-1953
Sabbatical leave to Institute of Ophthalmology, London, England 1959-1960.

Member of Societies:

American Society of Zoologists
American Physiological Society
Optical Society of America
American Association for the Advancement of Science
Biophysical Society
Association for Research in Ophthalmology
American Academy of Neurology

Committees:

Research Counsel, San Diego Zoological Society
National Counsel to Combat Blindness
Study Section, U.S. Public Health Service
Committee on Vision, National Research Council
Editor, Vision Research

Research Interests:

Insect metamorphosis
Insect metabolism
Nerve physiology and pharmacology
Physiology of vision
Biochemistry of vision
Color vision

Family:

Married to Fiona Clyde
Three children:
Richard, 13 M
Monica 10
Adrian 7

Publications:

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7. Affidavit of Adrian Gross, D.V.M. and curriculum vitae (Dock. No. 185), and excerpts of testimony in *Ealy v. Richardson-Merrell, Inc.* (Ex. 26 to Pltfs.' Opp. to Summ. Judg.), filed Aug. 22, 1989, and Sept. 28, 1989

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UNITED STATES DISTRICT COURT
For the Southern District of California

NO. 84-2013-G(I)

WILLIAM DAUBERT; JOYCE DAUBERT, Individually and as Guardians Ad Litem for JASON DAUBERT, a Minor,
Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES 1 through 50 Inclusive,
Defendants.

NO. 84-2929-G(I)

MICHAEL SCHULLER, ANITA DE YOUNG, and ANITA DE YOUNG as Guardian ad Litem for ERIC SCHULLER,

Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES 1 through 50. Inclusive,

Defendants.

[2] **AFFIDAVIT OF ADRIAN GROSS**

1. My name is Adrian Gross. I am a veterinarian. After my four year combat service in the British Army, I matriculated in 1946 at the University of London, England, and then received my Bachelor's Degree at the University of Manitoba in 1949. I did additional postgraduate work at the University of Manitoba and then received my DVM degree and veterinary surgeon degree, in 1954. I then proceeded to do advanced pathology training at Ohio State University where I received a Masters' Degree in pathology and completed veterinary pathology courses. After that I took a number of postgraduate courses in statistics and biometry at the Michigan State University. Biometry is a branch of statistics that deals with measurements arising in biological fields. The M.Sc. degree from Ohio State was in pathology which involved the study of the disease process in animals and humans. I have been licensed to practice veterinary medicine continually since 1954. I was subsequently accredited by the United States Department of Agriculture in the field of veterinary medicine.

As concerns pathology, I have been employed as a pathologist with the United States Public Health Service, and in private research organizations. I then became Chief of Pathology of the Food and Drug Administration in 1964 and held several other positions there during the next 15 years. I began my service with the FDA in 1964

as Chief of

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Pathology which involved supervision of a number of professional pathologists, (both physicians and veterinarians) who were engaged in examination of tissues during autopsies on animals. Following this, I next became the Deputy Toxicological Advisor. Toxicology is the medical discipline that deals with the adverse effects on health elicited by poisons. I then became the Assistant Director for Program Coordination which involved coordinating research on the safty of drugs. After that I became the Associate Director for Preclinical Investigations which required me to go around the country and supervise other scientists and audit toxicology studies. An audit is a process where one looks into the reliability of reports submitted to the FDA by the manufacturers of drugs. Our duties involved in the most paramount fashion examining the reliability of reports on research for the purposes of safety of drugs. An audit is an investigation where the reliability of reports is assessed at the site where the report has been prepared, i.e., in the laboratories of the manufacturers. The duties included examining the laboratory notebooks of raw observations and making sure that all observations were promptly and fully reported, checking of the facilities, checking the equipment and checking out the laboratory. My position required that I be satisfied with the way the operations were being run at the various laboratories, that the technicians knew what they were

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doing, and checking on credentials, training, supervision of the personnel involved in such studies.

Thereafter I transferred at the Environmental Protection Agency where I became Chief of the Toxicology Branch where I supervised many toxicologists. In 1980 I was promoted to Senior Science Advisor, a position I still hold.

I am giving this affidavit as I have given testimony on Bendectin in the past purely as a citizen and not as a representative of the United States Government.

I have been credited with a number of publications in the field of pathology and statistics but that is not the principal function of either the FDA or the EPA.

I am a member of the American Statistical Association, and

during my career with the FDA and the EPA I have consistently used formal statistical analysis of toxicology results; the aim of such analyses is to determine the relationship of a drug to a toxic effect.

I have also had training in embryology.

I am familiar with the subject of teratology because it encompasses the same areas that I have worked in during my career including embryology, pathology, statistics, and teratology. Teratology testing is simply another kind of toxicity test which focuses on events very early in life and shortly after birth.

I have as part of my duties analyzed data that have been collected for the purpose of determining whether or not

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a drug causes birth defects. That has been my function with the government in the past. In my experience with the government I have received commendations and awards from the United States Government including the Commissioner of Food and Drugs and various members of Congress.

2. I have performed an evaluation of the results arising in various animals studies that have been done involving the drug Bendectin and its components and in so doing I have utilized the methods and methodology that would generally and reasonably be accepted by those people who deal in the areas of evaluation of drugs for safety purposes and for toxicity purposes and for teratology purposes. I have reviewed what has been represented to me as being all of the animal studies pertaining to Bendectin and its components that were performed by Richardson Merrell, a/k/a Merrell-Dow. Those studies bear the numbers 63-01, 63-02, 63-27, 63-28, 63-29, 66-01, 66-02, 66-05, 66-07, 66-12, 75- 12, 75-13. I have also reviewed laboratory notebooks bearing the numbers 401T and 458T which pertain to studies 63-28 and 66-05. I have further reviewed animal studies performed outside the premises of Merrell known in this litigation as the following studies: "Rolle"; "RTI"; "McClure"; "Hendricks I and II"; and others. I have also reviewed data that were submitted by Richardson-Merrell, a/k/a Merrell Dow, to the FDA and various other memoranda.

I have further submitted a detailed analysis

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of the results arising in such studies to counsel representing all parties to this action.

3. It is my opinion within a reasonable degree of certainty that from reviewing the animal studies identified previously and based upon my experience, education and training and utilizing the methods and methodology that are generally and reasonably relied upon by anyone analyzing such studies for the purpose of determining whether or not a drug has a toxic effect, or a teratological effect that the doxylamine succinate component of Bendectin is in fact a teratogen. By that I mean that it is capable of causing birth defects.

It is also standard practice in analyzing such animal data to do statistical analysis of the type that I have performed. Basic textbooks on the subject of teratology, such as Wilson's Handbook of Teratology, clearly show that a teratogenic effect or a toxic effect manifests itself by death, malformation, growth retardation and functional disorder. These are the manifestations of abnormal development which is caused by toxic substances such as teratogenic agents.

4. The purpose of doing animal studies is to determine as best as one can what will be the likely results in the human. There are a number of well-known reasons for studies in humans to have only limited usefulness in the process of establishing the safety of new drugs. It is

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largely due to this reason that studies in animals become critically important in this respect. One can then utilized one's education, training and experience by using generally and reasonably accepted methodology in an analysis to reach an opinion as to whether or not the drug would be a toxic substance or a teratogenic substance in the human. Animal studies in such a setting are not performed for the express purpose of determining the effect of a teratogenic agent on the animal, but rather on the likely safety of the agent for the human.

Further, the evaluation of results from a teratology study are in no way different from the evaluation of the results of any other toxicological study. The techniques that one uses are identical.

5. Having reviewed the animal studies conducted by Merrell, one cannot conclude from any of those studies that Bendectin is safe from a teratogenesis point of view. Moreover, as I further explain below, some of those studies indicate beyond a reasonable doubt

that Bendectin does cause birth defects and is, therefore, a clear cut or unequivocal teratogen.

6. When one refers to notebook 458T and 401T, which are the notebooks pertaining to study 63-28 on rabbits, one can easily note that the results in the notebooks are different from the results in the reporter's studies. I have conducted an audit of the notebooks and the studies in

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the same fashion that I have utilized and with the same methodology that I have utilized during my experience of doing such audits with the Federal Government. Having performed such audit, it is my view that the data collected in the notebooks clearly reflect that Bendectin was causing teratogenic effects in the rabbits being tested. Moreover, I have read memoranda from the company that also indicates that the principal scientist directing such studies at Merrell also concluded that at the very least additional studies were necessary. As far as I know, additional such studies were in fact not carried out at Merrell. Specifically, the animal studies on the rabbits in study 63-28 and in the notebooks, showed that there was an effect on the cartilage development in the ossification area such that it was not developing properly. This was a teratogenic effect on the skeletal system.

An examination of other studies done by Merrell with respect to doxylamine succinate continues to show increasing problems with the doxylamine succinate as concerns cell toxicity and teratogenicity and further shows that as the dosage increased, so did the teratogenic effects. This is another clear manifestation of teratogenicity.

7. From reviewing the additional studies, one finds that other abnormalities were discovered in studies done outside of the company. Namely, diaphragmatic hernias and other defects (Rolle); reduced weight in the fetuses

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(McClure); heart defects (Hendricks); and reduced ossification centers to a statistically significantly degree such that the chances were only one in one thousand that the drug Bendectin did not cause the defect (RTI). In the RTI study, the ossification centers, or areas that develop into bone, were significantly reduced.

Further, the animal studies that were performed by Merrell also had animals that had malformed limbs as well as other malformed bone structures.

8. It is standard practice to make extrapolations or render opinions as to the effect a drug would have on a human based upon animal data.

9. Thus, when having reviewed the data mentioned heretofore including the notebooks, studies done within the company and those done outside the company and utilizing my education, training and experience, there is no doubt whatsoever, certainly far beyond a reasonable doubt, and certainly within a reasonable degree of scientific certainty that Bendectin causes birth defects and is teratogenic in various animals. Therefore, I can state that based upon my education, training and experience within a reasonable degree of certainty, and in fact beyond any reasonable doubt, Bendectin and its component doxylamine succinate has the capacity to interfere with the normal development of cells in the human being and thus is a teratogen in the human being, at the normal therapeutic dose.**[10]**

10. I would like to point out that this opinion is further that the drug is a teratogen at the normal human therapeutic dose. Merrell repeatedly notes that animal studies involved dosages higher than those utilized in the human. There are many reasons for this. However, I would like to point out that this is the standard way of testing drugs in animals to determine their effect on humans. It is well known that individual humans have different levels of susceptibility to different substances such as drugs. So do lower animals. Rather than testing thousands and milllons of animals, the standard practice is to test at dosages that would be considered to be higher than the normal human dose and then extrapolate to the human. That is the generally and reasonably accepted methodology in the field.

11. I have further recently examined data provided by defendant that concerns the number of sales tablets sold in Canada over a period of time and an article by Iskenius-Froster, et al. which explores more than one in one-quarter million births in Canada during the period of time that Bendectin was and was not on the market in Canada. The Iskenius-Froster information details the rate of limb defects in those one in one quarter-million births. Having

performed the statistical analysis upon that data just mentioned in the same fashion that statistical analysis are generally performed in order to determine whether or not there is a statistical association between an agent and an

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effect such as a drug and a birth defect, one can see that there is in fact a statistically significant association that is highly significant between the sales of Bendectin in Canada and limb reduction defects. This is another piece of information that is useful which would generally and reasonably be relied upon to help determine whether or not a drug is a teratogen.

12. Based on the foregoing data concerning the Iskenius-Froster data and the data from the company concerning the sales of Bendectin, it is my opinion that within a reasonable degree of certainty that such information contributes to the knowledge that Bendectin does in fact cause birth defects in the human.

13. Moreover, the United States Government has identified in public documents that Bendectin is a developmental toxicant which is another term for teratogen. It is my strongly-held view that the animal studies do indicate clearly and unambiguously that Bendectin is a developmental toxicant.

14. In sum, based on my education, training, experience, review of the animal studies on Bendectin and its components including doxylamine succinate, it is my opinion within a reasonable degree of certainty that at the normal therapeutic dose Bendectin is a teratogen in numerous animal species as well as in the human, utilizing generally and reasonably accepted methodologies and that the Iskenius-

[12]

Canada confirms this opinion.

/s/
Adrian Gross, D.V.M.

[notorization omitted]

UNITED STATES DISTRICT COURT
For the District of Columbia

NO. 83-3504

Sekou Ealy, et al.,

Plaintiffs,

v.

Richardson-Merrell, Inc.,

Defendant.

July 18, 1987
Courtroom 7
Washington, D.C.

The above-entitled matter came on for trial before the Honorable June L. Green at 9:55 a.m.

Reported by: Bonnie L. Gahagan

Dawn Copeland
Official Reporter
Phone (202) 535-3397
Room 4806-B, U.S. Courthouse
3rd and Constitution Avenue, N.W.
Washington, D.C. 20001

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PROCEEDINGS

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(Jury not present.)

THE COURT: I see where I am a little bit early. Discussion off the record.)

(Jury present.)

THE COURT: Good morning, ladies and gentlemen.

THE CLERK: Civil Action Number 83-3504, Sekou Ealy, et al., versus Richardson-Merrell, Inc. For the plaintiffs, Barry Nace, John Sellinger; for the defendant, Mark Austrian and Patrick Coyne.

MR. NACE: Your Honor, at this time the plaintiff would call Dr. Adrian Gross.

Whereupon --

ADRIAN GROSS,

a witness, called for examination, having been first duly sworn, was examined and testified as follows:

DIRECT EXAMINATION

BY MR. NACE:

Q. Good morning. Give us your full name, please?

A. My name is Adrian Gross, G R O S S.

Q. Doctor, what is your current place of

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employment?

A. I work in the United States Environmental Protection Agency.

Q. Have you previously worked for the FDA, Food and Drug Administration?

A. Yes, sir.

Q. Right at the beginning, are you appearing here on behalf of the Food and Drug Administration or the Environmental Protection Agency?

A. No, sir, I am not. I appear as a private citizen.

Q. Now, I said Dr. Gross. Are you a medical doctor?

A. No, I am a veterinarian, veterinarian medical.

Q. Let me ask you, doctor, where do you live?

A. I live in Maryland, Silver Spring, Maryland.

Q. Can you tell us where you went to college and where you had your post-college training?

A. Yes, sir. I matriculated in 1947 at the University of London, England, and then got my Bachelor's degree at the University of Manitoba in Canada in 1949. Then I took an additional year of postgraduate work there, and then went to veterinary

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school also in Canada, graduated in '54 with a D.V.M. degree, veterinary surgeon degree.

Q. What is the difference between D.V.M. and veterinary in surgery degree?

A. There is no basic difference. It just so happens that the one gets sort of a dual degree in Canada where the D.V.M. comes from the University of Toronto where the veterinary of college is veterinary of surgery, same courses.

Q. What year did you complete those two degrees?

A. In 1954.

Q. After you did that, what did you do?

A. I went into advanced pathology training and this was at the Ohio State University in Columbus. I got a Master's degree there in pathology and at the same time completed my work for -- the required work for --

Q. Let me pull this down for you, make it a little more comfortable.

A. Completed there in veterinary pathology and then I took a number of postgraduate courses in statistics and biometry at the Michigan State University.

Q. Let me stop you. What is biometry?

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A. Biometry is a branch of statistics that deals mostly with biological quantum, numbers and measurements arising in biological fields, as opposed to statistics in economic statistics.

MR. NACE: I may have pulled the microphone down too low.

THE COURT: I think he just let his voice drop.

THE WITNESS: I am sorry.

Q. Okay. Did you get a Master's degree?

A. Yes, from Ohio State.

Q. That was in what field?

A. In pathology.

Q. In pathology, is that human pathology, animal pathology or exactly what is it? Is it the same?

A. Pathology is the same. I took courses in both the medical school and in the veterinary school, carried out autopsy on animals, helped -- and also helped in autopsy with humans.

Pathology is a branch of medicine that deals with the nature of the disease process which is the same in animals and humans.

Q. What do you mean by that, that it is the same?

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A. Well, the basic mechanism by which disease arises is the same in all mammalian species. The humans have some of the same diseases as animals. Some diseases in humans don't have counterparts in animals and vice versa, but the basic fundamental process of disease is the same.

Q. Okay. Now, did you at any time have any military service?

A. Yes.

Q. Where was that?

A. That was in the British Army during the war, World War II, before your time. That was four years combat service in the British Army.

Q. Then have you been licensed to practice veterinary surgery, veterinary medicine?

A. Yes.

Q. Where have you been licensed?

A. I was licensed in '54 in Ontario and Ohio, Indiana, Michigan.

Q. Have you eventually been accredited by any organization?

A. No -- well, yes, I was accredited by -- I thought you meant something else, but I was accredited by the United States Department of Agriculture. I was accredited by examination.

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Q. What does that mean?

A. I suppose it means that I can carry out -- I have never done this actually, it is a long time ago, but what it meant, in my understanding, is that I could carry out all of the regulatory functions that the United States department of Agriculture expects of their veterinarians.

Q. Have you been employed as a pathologist?

A. Yes, sir.

Q. By whom have you been so employed?

A. Well, I started out with the United States Public Health Service in Cincinnati, the Occupational Health Service as it was called there when I was the research pathologist and then continued in a number of private research organizations such as the Arthur D. Little Company in Cambridge, Massachusetts, Microbiology Associates here in Bethesda and then became chief of pathology of the Food and Drug Administration in 1954 and then held some other titles for about 15 years in 1979.

Q. Let me ask you about your employment with the Food and Drug Administration.

A. Yes.

Q. When did you start there?

A. In 1964.

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Q. When you started there, what was your position?

A. Chief of pathology.

Q. As the chief of pathology with the FDA, what did your duties involve?

A. Well, I was chief of the pathology branch which meant that I supervised a number of professional pathologists, both human medical and veterinary medical who were engaged in examinations of tissues, doing autopsy on animals, so I was their supervisor.

Q. Okay.

A. Then, of course, we had a laboratory with a number of technicians to support such pathologists.

Q. Did the FDA do its own teratology testing?

A. Yes, and still does today, some of it, yes.

Q. Would you explain a little bit about that?

A. What a teratology test is?

Q. Well, what they do.

A. Well, they have a research program, both in house and

also they contract certain pathology studies at outside institutions, but what they do in-house is expose a variety of animals to test agents as we call them and food additives, drugs, so on, and we as pathologist have the responsibility of

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examining the animals for both defects and so on.

Q. After you served as the chief of pathology branch at the FDA, what did you do next at the FDA?

A. Next I became the deputy toxicological advisor working under Dr. Fitzhugh who was the toxicology advisor. I was his deputy, meaning his flunky. He gave me all sorts of jobs to help him with his jobs in the national and international agencies that he belonged to. Mostly I assisted him in that.

Q. I don't think we have had anybody explain what toxicology is yet. What is toxicology?

A. Toxicology is a medical discipline that deals with the adverse effects on health elicited by certain poisons. That is, the word toxic means poisonous. One can also look at toxicology as the same as -- or at least in the sense that the FDA did, they tested drugs, food additives, pesticides, cosmetics for safety, so toxic is the reverse of safety, so the experimental testing program is part of toxicology, trying to define what are the safe or the toxic properties of whatever they are testing.

There are a number of other stimuli or other agents that produce disease in animals or humans such as infectious organism, bacteria,

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viruses, on. This is not part of toxicology.

Toxicology is typically chemical agents, such as drugs, pesticides and so on.

Q. After you served there as a deputy toxicology advisor, what was your next position with the FDA?

A. Let me see. The title of that position is always a mouthful. I was assistant director for program coordination, I believe.

Q. What did that mean? What did you do?

A. Well, I was supposed to coordinate the research into safety of drugs.

Q. Coordinated it?

A. Yes, coordinated it.

Q. Then after that what was your position?

A. And then I became the associate director for preclinical investigations.

Q. What did you do in that position?

A. That was largely a job of -- I was, again, the chief of a branch and the associate director of a division of which the chief was Dr. Kelsey, and my job was at that time to go around the country and supervise all of the other scientists that did that, go around the country and audit studies in toxicology.

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Q. What did you do to the studies?

A. Audit.

Q. What is an audit?

A. An audit is a process where one looks into the reliability of reports submitted to the FDA.

Let me explain that under the food, drug and cosmetic act, the principal law that governs the mission of the FDA, the responsibility for testing the safety of drug products rests with what we call the regulated industries, meaning the manufacturers of the drug. They are the ones that are responsible for testing the drugs for safety.

Q. As opposed to the FDA?

A. Yes.

Q. Okay.

A. They do that themselves, and they are expected to do that, and then they submit reports to the FDA, and it is on the basis of such reports that the agency, A, approves or does not approve the drug for marketing, and B, if it approves if for marketing, it states what are the conditions for marketing, what labeling ought to be attached to a drug or what restrictions are to be imposed.

Q. Is that since the Kefauver Act?

A. Yes, 1960, Kefauver Act.

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So the FDA acts on the basis of such reports that it gets from the manufacturers or the regulated industries, but then there is always the question of how do we know such reports are reliable, and that is the function of the audit where one goes periodically on some of these reports, one goes into the laboratory which executed

the study, and the private industry, and one carries out an audit of the report against the actual observations that were made which are usually not submitted to the FDA.

Q. What is the difference between an audit and perhaps a review?

A. There are two different things. A review is carried out at headquarters by physicians, toxicologists, pharmacologists, chemists, they review the reports in order to assist the safety of the drug. That is the review function. They sit right here in Washington and review and evaluate the results, and an audit is an investigation, if you want, where the reliability of the report is investigated right at the site where it is executed.

Q. You did that?

A. I did that, yes.

Q. Would you actually look at the company's various notebooks?

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A. Yes, you look at the notebooks and see that all of the observations are properly reported, you check their facilities, is this the right sort of place to carry out studies like that, do they have the right equipment, are [their] laboratories the way they ought to be.

Q. Did you look at the animals themselves that may have been involved?

A. Right. Well, the animals we usually don't see because the audit is carried some time after the study, but we see other animals that are in progress, we look at their operation, we look at how their technicians work, you know, in the normal course of their duties, do they know what they are doing, what are their credentials, their training, their supervision, that sort of thing.

An audit is very much like an IRS audit. You are sending your income tax return, and if they have questions about this, you are supposed to explain what you did.

Q. Now, after you held this position, associate director preclinical investigations at the FDA, what was your next position?

A. Then I transferred to the Environmental Protection Agency where I became the chief of the

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toxicology branch which is a branch that does strictly what you term

review and evaluation in toxicology, so I was a supervisor of a large branch there with many, many toxicologists, and this went on for a year or so, and since 1980 and currently I am the senior science advisor.

Q. Well, let me ask you then what a senior science advisor has for duties?

A. That is easy. He gives advice.

Q. Besides give advice, in what areas?

A. Not in the stock market, in scientific areas, in my case toxicology, pathology, whatever. It is in the scientific areas.

Q. Have you done any publishing in the field of pathology and/or statistics?

A. Yes, a limited number. The material that we deal with certainly at the FDA and also in the EPA, the studies that we review and so on are largely confidential, so one is not at liberty to publish on one's work as a general rule.

Now, I have published one or two papers that deal mostly with methodology either in pathology or in statistics, but, as I say, both at the FDA and the EPA, what we work, publication is not one of the things one is expected to do.

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Q. Now, are you a member of the American Statistical Association?

A. Yes, I am.

Q. In work that you have done over the last -- well, with the FDA and the EPA, in what way are statistics used? How does that relate, I should ask, to biometry?

A. Well, it is really all biometry because we are dealing with data collected from biological systems, right?

I should say that statistical analysis, biometric analysis, statistical analysis of the results emanating from toxicology trials, typically have to be subjected to statistical analysis in order to reach an assessment, whatever we have tested, say a drug, is it or is it not safe, and it may be safe under certain conditions, but not safe under some other conditions, so this assessment of how safe an agent on test is based on the experimental data needs statistical analysis. Without that, one cannot conceive -- at least I can't conceive -- how a study such as this can be made. Sometime[s] a formal statistical analysis may not be necessary because the results are so clear-cut,

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either clear-cut negative or clear-cut very positive, either one is very safe or not very safe, so one may not need to go through the statistical analysis, but in actual fact, the process of evaluation always involves statistical analysis. It may not be a formal one because, as I say, the results may be obvious, but it is an implied function of assessing the safety of the chemical agent.

Q. Doctor, you told us a little about your pathology training. Have you had training in embryology?

A. Yes, when I was in school we had training in embryology, yes.

Q. Have you used that training in embryology throughout your career?

A. I have used it, but I wouldn't call myself primarily an embryologist, but I have used it, yes. In fact, one has to have an understanding of embryology to be a pathologist in the first place. Everything derives from an embryo or the tissues, and one has to know what is normal, what is abnormal in a developmental sense of an organism, but I wouldn't call myself an embryologist, but I have been trained in it.

Q. Are you familiar with the phrase

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teratology?

A. Yes, I am.

Q. What is teratology?

A. Teratology is sort of a term for -- it is a fairly new term. When I was in school there was no science of teratology, but now some people call themselves teratologists and there is a Journal of Teratology, there is a society, and members of it, I am not a member of a Teratology Society, but there are the people that deal with developmental types of defects, developmental toxicants or teratogens.

It is, as I say, a new term that I can't tell you exactly when it came into being, but sometime in the late '60s I would guess, perhaps early '60s, somewhere around that time, but teratology is, to my view, that branch of science that deals with abnormal development.

Q. What areas of science does it utilize?

A. I am sorry?

Q. What areas of science does it utilize?

A. What does it utilize?

Q. What teratology utilizes.

A. It utilizes certainly embryology, utilizes pathology, utilizes other parts of toxicology. Teratology test for a drug, let's say, is really

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just another kind of toxicity test. It is a test to determine the safety of this drug from a particular point of view, and that is, it focuses on the perinatal stage of development. In other words, it focuses on events very early in life, before life in the sense and shortly after birth.

Q. Let me ask you, have you yourself examined animals for birth defects?

A. Yes, sir.

Q. Could a teratologist do that, also, someone who calls himself a teratologist?

A. Yes, if he has training in this kind of pathology, yes.

Q. Have you analyzed data that has been used or collected for the purposes of determining whether or not a drug causes birth defects?

A. Yes.

Q. Has that been part of your function with the government in the past?

A. Yes.

Q. Do you consider yourself to be an animal teratologist?

A. No, not strictly.

Q. Why not? Why not?

A. Well, as I have said before, I am not

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regarded as such by the government as a teratologist, primarily a teratologist, although I have worked in this field, this is not my sole interest. My interest is largely in pathology, and pathology is broader than just teratology. Teratology, it seems to me, they restrict themselves to the areas, as I mentioned, limited to anomalies of development, early pathology changes. They don't go beyond that. I have never considered myself as a teratologist. As I said, I am not a member of the society, and that is the way I view myself

and others view myself.

Q. Are you familiar at all with how labeling takes place with drugs?

A. Yes.

Q. First of all, how have you become familiar with that?

A. Well, I put in 15 years with the FDA. If I wouldn't be familiar, I earned my money for nothing there.

Q. What kind of knowledge would you have with respect to labeling and safety?

A. Well, I would say most of what the Food and Drug Administration does in the area of drugs is related to labeling. As I was saying before, it is the responsibility of the agency to approve or

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disapprove of new drugs, and if they approve, they have to focus on whether the drug is properly labeled, so, the mission, this mission of the agency is the ultimate result of the efforts of practically all of the scientists that they have there that concern drugs, Bureau of Drugs, Bureau of Foods and so on. It is the ultimate responsibility and ultimate function of the agency and I would say most of the efforts and review of the scientists is aimed at that goal.

Q. Have you in the past given testimony in the field of adequate labeling?

A. Yes.

Q. Have your received any commendations or awards from the United States Government or agencies?

A. Yes, I have.

Q. Would you tell us about those, please?

A. Well, I have received personal commendations from the Commissioner of the Food and Drugs in 1970 some time, '75 or '76. I have received accommodations from Senator Kennedy, Ted Kennedy, who was the chairman of the Subcommittee on Health that same time, '76 or --

Q. Was that in response to a particular drug being investigated?

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A. Yes.

Q. We are not talking about Bendectin, so we are clear on

that?

A. No, it wasn't Bendectin. It was a series of drugs made by a single manufacturer at the time.

Q. Are you still called upon by congress and congressmen?

A. Yes, I was. As a matter of fact, just a couple of weeks ago they called me there to testify before them. They were looking into whether the approval for a drug was properly given by the FDA, and they asked me to testify in this regard. They sent me whole huge box full of material, documents, studies, reviews, and then they asked me to testify before them a few years ago.

My agency loans me out like a library book to other agencies who have problems. I am regarded in the agency as an international expert in the evaluation of safety of chemical agents, so other places periodically ask me.

The Food and Drug Administration asked me to help them after I was gone from their regular employment, so I spent time there testifying in trials for them and so on, and all of my testimony is always scientific. I testified as an expert in

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the area of science of the safety of drugs and other agents. I don't just give opinions. It is all based on review and evaluation of data.

Q. Doctor, have your performed an evaluation of various animal studies that have been done involving the drug Bendectin?

A. Yes, I have.

Q. In performing those reviews, have you utilized the methods and methodology that would generally and reasonably be accepted by those people dealing in the areas of evaluation of drugs for safety pruposes?

A. Yes.

MR. NACE: Your Honor, I would offer Dr. Gross as an expert in the field of pathology, animal pathology, toxicology, biometry and the evaluation of safety of chemical agents.

THE COURT: Questions.

MR. AUSTRIAN: Yes, I do, your Honor.

EXAMINATION ON THE VOIR DIRE

BY MR. AUSTRIAN:

Q. Good morning, Dr. Gross.

A. Good morning, Mr. Austrian.

Q. Now, as I understand it, you do not practice medicine or have a license to practice

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medicine; is that correct?

A. That is correct.

Q. Now, with the exception of a short period 20 years ago, you have never really practiced veterinary medicine; isn't that true?

A. That is true.

Q. Now, you are familiar with the concept of board certification?

A. Yes, I am.

Q. Board certification is available to individuals who practice in veterinary medicine that have additional training in certain areas; isn't that correct?

A. That is right.

Q. You had requested a training period for approximately 10 months to work in various institutions to prepare you for a certified examination; isn't that correct?

A. Well, it is partly correct, but not quite. From your question I get that this was the main purpose for my -- for that period of training from about 10 months in the early ' 70s, 1970, '71. The truth is that I went around, it was my sabbatical leave and I felt I ought to sort of recharge my batteries in pathology with the latest information,

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and I asked that I spend some time at a number of institutions in pathology, and I thought that with this I might also get -- prepare myself also for the examination for baord certification, but this was sort of frosting on the cake, I would say, but I eventually decided that I don't need it and I didn't want to be examined.

Q. You did not take the baord certification in veterinary pathology?

A. No, I didn't.

Q. You were not certified in the field of veterinary pathology; is that correct?

A. That is correct.

Q. You are not board-certified in any field; is that correct?

A. That is correct.

Q. You do not have any advanced degrees from a recognized university in either statistics or biostatistics; isn't that correct?

A. That is correct.

Q. You do not consider yourself to be a statistician, do you, Dr. Gross?

A. That is correct.

Q. As I understand it, you graduated from the University of Manitoba, 1949?

* * *

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Drug Administration; isn't that correct?

A. From '64 to '68, yes, correct.

Q. Now, at that time you did not have principal responsibility for evaluation of teratology data, did you, doctor?

A. That is correct.

Q. The evaluation of teratology data was done be reviewers at the Food and Drug Administration who are mostly pharmacologists and toxicologists; isn't that correct?

A. That is correct.

Q. You did not do any animal teratology testing in that position, did you, doctor?

A. Well, as I explained earlier, I participated in such trials by doing the pathology examination of the newborn which is the critical aspect. Now, I did not direct such studies, I didn't originate them, I didn't -- this was my responsibility, but in fact, I participated in such tests.

Q. Let me ask again: You did not yourself, you yourself, have the responsibility, and did not do an animal teratology test while you were chief of pathology; isn't that true?

A. I don't know what you mean by you did, I

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did such tests.

THE COURT: What kind of tests did you do, doctor?

THE WITNESS: Well, your Honor, the animals are put on tests by some scientist, if he decides what tests should be done and the animals are to be dosed to such an agent for such amounts, and then one waits to see what happens. These are usually female

animals that are pregnant and that give births to litters of pups and then they are examined for any birth defects.

Now, I participated in precisely that, examining the animals. This is what I did, and I have explained this.

Now, the actual putting --

THE COURT: These were what, newborn baby animals?

THE WITNESS: Yes, ma'am, yes, these were animals. These are experimental studies.

THE COURT: What kind of animals were they?

THE WITNESS: Well, there were rabbits, rats, we used -- I am trying to think of the name of this animal. It just escapes me now. It is another species of animals that we used and the name just escapes me now. Gerbils, some monkeys I have done,

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examination of newborn monkeys, and that is what I did.

MR. AUSTRIAN: May I continue?

THE COURT: Yes.

MR. AUSTRIAN: Thank you, your Honor.

BY MR. AUSTRIAN:

Q. Now, from 1968 to '69 I believe you testified you were deputy toxicology advisor; is that correct?

A. Yes, sir.

Q. You did not do any teratology testing in that position, did you?

A. No.

Q. 1970 to '74 you were assistant director for program; is that correct?

A. Yes.

Q. Your responsibility in that position was mostly coordinate the research activity of the Bureau of Drugs?

A. That is right.

Q. At that time you did not do research in teratology or evaluation of teratology data in that position; isn't that correct?

A. That is correct.

Q. You have never at any time been the one

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who has actually selected or determined what doses were to be given in an animal teratology study; isn't that correct?

A. Absolutely correct.

Q. In fact, you have never at any time been responsible for the design or the execution or the initiation or supervising of any animal teratology studies; isn't that correct?

A. That is correct, yes.

Q. From 1975 to 1979 you were associate director for preclinical investigation at the Food and Drug Administration, correct?

A. Correct.

Q. Your investigation was limited to whether the report was properly done and reliable, true?

A. Yes.

Q. However, the primary responsibility for evaluating an animal teratology study to see if it raised a safety concern was that of another division of the Food and Drug Administration, the reviewing division; isn't that correct?

A. Sir, there were many reviewing divisions, there still are today, in the Bureau of Drugs. Each division reviews drugs in a particular area. There is a review division that deals with cardiovascular

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drug, another one with infectious agents, so there are many reviews.

In my capacity as pathologist, I was frequently asked to help the primary reviewers -- I was not the primary reviewer, I will grant you that.

MR. AUSTRIAN: Your Honor, I believe my question was very specific. I asked him isn't it the fact that the primary responsibility for evaluating animal teratology studies to see if it raised a safety concern was that of another division at the Food and Drug Administration, the reviewing division.

Q. Isn't that correct, doctor?

A. Sir, there are many reviewing divisions, and I am saying to you, again, and you are right, that is their primary responsibilities.

Q. Thank you, doctor.

A. However --

MR. AUSTRIAN: Your Honor.

MR. NACE: Let him explain.

THE COURT: Did you serve in the other branches or

with them ever?

THE WITNESS: I did not serve in a reviewing division, but I was called upon in a consulting capacity to help in the evaluation of

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drugs from a safety point of view in many different aspects, including teratology.

MR. AUSTRIAN: Continue? Thank you.

BY MR. AUSTRIAN:

Q. In 1979 you went to the EPA as senior science advisor; isn't that correct?

A. No, I believe I testified that I went there as the chief of toxicology.

Q. I am sorry. That deals mainly -- the EPA deals mainly with pesticides and not drugs; isn't that correct?

A. Yes.

Q. Now, you have never actually done, I believe we have established, an animal teratology study, true?

A. I have never initiated, supervised or originated a teratology study.

Q. Or carried one out?

A. Well, I have carried out parts of it.

Q. You never carried out a whole teratology study?

A. Well, I don't think anyone does. I carried out the pathology functions.

Q. All right. Now, you are not generally familiar with substances which are teratogenic in

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animals, are you?

A. No, I am not.

Q. That is because you are not an animal teratologist, correct?

A. That could be, yes.

Q. There are people who actually do teratology studies and are known as animal teratologists; isn't that correct?

A. Yes.

Q. You are not a specialist in animal teratology, are you, doctor?

A. No, I am not.

Q. While you were at EPA, there was nothing that prevented

you from publishing articles of scientific interest, isn't that true?

A. As I was saying before, the work consists there of review and evaluation of the safety of pesticides in my outfit, and I also explained that most of these data are confidential. You cannot publish them. Publication is not encouraged there. Now, does that answer your question?

Q. No. Was there any legal requirement that if you were doing studies or had an area of scientific interest that prevented you from publishing?

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A. But that is not my function in the EPA to do research and develop new methods. That is not what I am doing.

Q. So the answer to my question is no?

A. Say the question again.

Q. There was no legal requirement while you were in the government from publishing articles of general scientific interest; isn't that correct?

A. If that were my job, that would be true. As it happens, it isn't my job.

Q. You do not have any teaching appointments at any academic institutions, do you, doctor?

A. That is correct.

Q. You have never had any such appointments; isn't that true?

A. Yes, that is correct.

Q. You have never published any articles in the scientific literature dealing specifically with the subject of teratology or birth defects, isn't that correct?

A. That is true.

Q. You are not a member of any professional organizations dealing with the study of birth defects?

A. That is right.

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Q. You do not consider yourself to be an expert on FDA regulatory requirements; isn't that correct?

A. Well, I don't know what an expert is in FDA regulatory requirements, so I can't answer that question. I just don't know that there are such people. I would say that I am familiar with the FDA regulatory requirements.

Q. I am sorry?

A. I am familiar with the regulatory requirements. I don't consider myself an expert, but I don't know who is an expert.

Q. Whether somebody else may be, you don't consider yourself an expert in FDA regulatory requirements; isn't that correct?

A. I would say that I am familiar. I don't know what the word is -- I don't recognize this as a field of expertise. I certainly don't view myself as one, and I don't know anyone else who is an expert in this area. There is no such recognized expertise, as far as I am concerned. I am familiar with the regulatory requirements. I will let it go at that.

Q. You did not have any responsibility prior to 1976, though, with any kind of regulatory

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supervision or reporting requirements under the FDA acts; isn't that correct?

A. No, that wouldn't be correct at all. I know what the regulated industry is supposed to be doing and I knew what the FDA was supposed to be doing.

Q. That is not my question. Prior to 1976 you did not have any responsibilities in connection with the reporting requirements while you were at the FDA; isn't that correct?

A. I am sorry, Mr. Austrian, I lost the question, if you don't mind.

Q. Yes. You were aware that there were reporting requirements for submission of data to the FDA prior to 1976; isn't that correct?

A. Yes, that is correct.

Q. None of the things that you were doing at the Food and Drug Administration prior to 1976 involved supervising or overseeing whether companies had complied with the reporting requirements; isn't that correct?

A. Oh, I see what you are saying. Yes, that would be correct.

Q. Now, you are not a pharmacologist, are you, doctor?

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A. I am certainly not a pharmacologist. I work in the field

of toxicology.

Q. And you are not an epidemiologist, are you?

A. No.

Q. And you had nothing to do with Bendectin until 1986; isn't that correct?

A. That is correct.

Q. And the way you got involved with Bendectin is that you received materials from attorneys; isn't that correct?

A. That is correct.

Q. While you were either at the EPA or FDA, you had nothing to do with Bendectin; isn't that correct?

A. That is correct.

MR. AUSTRIAN: Nothing further on voir dire, your Honor.

THE COURT: Approach the bench.

(At the bench.)

THE COURT: What are you offering him as an expert in?

MR. NACE: Toxicology, pathology, review of animal studies and how they are done by the company, auditing and the safety of chemicals and drugs and biostatistics.

* * *

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A. Your question is, sir, how does one draw conclusions from observational data?

Q. Yes.

A. Well --

THE COURT: How do you in particular?

THE WITNESS: Well, I believe I do it the same way everybody else does.

A. That is subject the data to a scientific sort of judgment, what we have here. I mean is this agent safe or dangerous.

As I was saying, there are a variety of techniques one uses in this process, statistical techniques mostly, and one reaches a --

Q. I am sorry, could you repeat what you said?

A. The data have to be analyzed statistically. Let me explain so that it is very clear. Suppose one carries out a test, and typically

teratogenicity tests, there are a number of other safety tests, toxicology tests, they are done at four levels. One is a group of animals that receives nothing, nothing in the way of the agent on test, just his own food, diet and so on. These are called the control animals. Then there are three other groups. One receives a relatively low dose of the agent on test and then there is a medium dose and then there is a

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high dose. We have four groups, control, low, medium and high.

Birth anomalies, let's say, could be present in all of these groups. They could be present in the control group as part of a general background or toxic, noxious agents that are in the environment, and then at the next dose there may be some and there may be some at the medium dose and there may be some at the high dose. Well, how does one reach a conclusion, evaluation conclusion did the agent on test cause an increase in the incidence of birth defects or congenital anomalies?

In order to answer that question, one must carry our statistical analysis of the results. Without that it is inconceivable to me how one can reach any conclusion. Not just on birth defects, but on anything else. Does the agent damage the eye? Does the agent produce neuro-type effects? This is common to the whole field of toxicology.

Q. What do you look at to make those determinations?

A. Well, one has to compare the results in a prescribed scientific manner to answer the question are these results that we see here just results that one could expect from random occurrences, or are

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they due to the agent on test, all right? That is the crucial question here, and in order to answer that question, one has to carry out the statistical analysis of the results.

As I said before, without this it is inconceivable to me how one can answer the question is this agent safe or not safe.

Q. Does that kind of analysis answer the question of cause and effect?

A. Yes, sir, absolutely, and without this analysis, this question cannot be answered.

Q. Is this what you have been doing in the past?

A. I have been doing this for -- yes, for at least a couple of decades.

Q. A couple of decades?

A. Yes, sir.

MR. NACE: May I proceed, your Honor?

THE COURT: Yes.

MR. AUSTRIAN: May I voir dire?

THE COURT: Yes, all right.

EXAMINATION ON THE VOIR DIRE

BY MR. AUSTRIAN:

Q. Doctor, you are not generally familiar with the literature in animal teratology; isn't that

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correct, the published literature?

A. That is correct, I don't review that as a matter of routine.

Q. The statistical technique that you use, this statistical technique that you use, I am talking about the work you actually do at the FDA and EPA, you do not use that statistical technique in evaluating animal teratology studies; isn't that correct?

A. I wouldn't say that is necessarily correct because I may in fact have used that, and I look for whether the sponsors, the manufacturers have used that.

Q. I am talking animal teratology tests, doctor?

A. What about it?

Q. Let me ask it a different way.

The statistical technique you use, isn't it a fact that you have never seen anyone in the published scientific literature dealing with birth defects ever use it?

THE COURT: Ever use what? I am sorry.

Q. I will rephrase it. Isn't it a fact that the statistical technique that you use has never been used in any animal teratology study that has

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been published in a peer-review journal?

A. I can't answer the question to you, Mr. Austrian, because I do not make it a routine practice of mine to review what is

published, but I can tell you this: In teratology studies that come to the attention of the Environmental Protection Agency when I was the chief of toxicology and I supervised the people that reach these kind of evaluations, they are looking for these types of analysis that I am talking about, statistical analysis, because without such statistical analysis, it is impossible to reach a conclusion on the safety of the agents on test, and the answer to your question is one does expect in the way of such studies that come to my attention or come to the attention of the government. That is what we are looking for. If there are no such analysis, we do these analyses ourselves.

Q. Let me ask the question again. You use a statistical technique, not generally, but you have a specific statistical technique called a linear --

A. I am sorry?

Q. The statistical technique that you use is a linear regression analysis; isn't that right?

A. In parts of the data I use linear

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regression analysis. Other parts are different.

Q. I am talking about your statistical analysis, the way you use it in analyzing these tests?

A. I have used a variety of statistical analyses on the work I have done on Bendectin.

Q. I am going to cut through.

Isn't it a fact that you have testified in the past in response to this question on the technique that you have used that you have given these charts where you have -- I think you called it a computer program, where you come up with these linear regression lines, "Answer, Yes, sir."

"Question: You are not aware of any teratology study that has ever been published that uses the specific technique that you use; isn't that true?["]

"Answer: I am not aware of any, but then I don't know what weight you can put in that because I read very little."

Isn't it a fact that you were asked those questions and gave that answer?

A. I gave you the same answer today, Mr. Austrian.

MR. AUSTRIAN: Thank you. May we approach,

* * *

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dictionary with medical terms in it?

A. Yes, it is probably the best known.

Q. Does that have the phrase teratology in it?

A. Oh, you mean the dictionary?

Q. Right there.

A. Oh, I see. Teratology.

Q. How is it defined?

A. That division of embryology and pathology which deals with abnormal development and congenital malformations.

Q. Is that the area that you have worked in?

A. Yes, sir.

Q. Let me ask you then, also, doctor, what is a developmental toxicant?

A. Developmental toxicant is a synonym for a teratogen, meaning an agent that is toxicant to an organism around its birth, in the period of time surrounding its birth, shortly before and shortly after birth.

Q. Doctor, based upon your experience and your education, what are the signs of a teratogen in an animal study?

A. Yes, well, I will give you that definition as it was given in the textbook written by Fraser and Wilson, Wilson and Fraser I should say identify

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a teratogen.

Q. What is it?

A. I don't know if I recall it word for word, but basically they say a teratogen is any agent that can elicit or can produce one or any of the following: Birth defects in the accepted sense, a congenital anomaly or birth defect is something that one sees. It is an anomaly of structure or anatomy. That is one effect of a teratogen, or it can be death of the embryo or fetus. That is really the ultimate insult, you might say. It can also retard growth, retardation of growth is another manifestation of a teratogen, or it can manifest itself in an anomaly of function.

Q. What does that mean?

A. As opposed to -- well, it is the way an organism works

rather than the way an organism looks.

Q. Doctor, let me show you, first of all, what has been marked as Plaintiff's Exhibit 10, project report 6301. Have you reviewed that previously?

A. Yes, I have seen this, yes.

Q. In reviewing it, have you reviewed it in the same fashion and the same manner which you would generally review other laboratory data and reports?

* * *

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MR. AUSTRIAN: When people have experience with human beings, and this witness has no experience with human beings.

THE COURT: I think he has probably never been asked to make that determination in his job or the jobs that he has had. I think he has always been asked to see whether the tests were made in accordance with the usual standards for making the tests, and I doubt that he has ever been called upon to make this decision because I think that it has been undoubtedly made by somebody else.

MR. NACE: Can I explore that?

THE COURT: Yes.

(In open court.)

BY MR. NACE:

Q. Doctor, when these particular studies are done on animals, first of all, why are they being done?

A. Why are they being done?

Q. Yes.

A. I will tell you one reason they are not being done for, we are not interested in whether Bendectin is safe to rats, rabbits and mice. That is clear. They are done for only one purpose, to establish the safety of these products for humans.

[839]

Q. As a pathologist who has been with the FDA and the EPA, have you had occasion to participate in decisions as to the meaning of the kind of data that we have been talking about as applies to humans?

A. Yes, of course. That is what we are doing all the time.

I mean the object of doing these studies is to estimate, to evaluate, to assess whether these agents are going to be safe for humans. They have no other purpose. They are not done for the benefit of the animals.

Q. Can one make extrapolations then or conclusions from looking at the animal data to decide what would happen in the human?

A. Yes, sir, that is their purpose.

Q. How do you do that?

A. Extrapolate the safety to humans.

MR. AUSTRIAN: Objection.

THE COURT: Have you ever been called upon to make that determination in any of the positions that you have had? Is it somebody else who determines it from the data that you have?

THE WITNESS: There is no one else either at the FDA or the EPA that makes such assessment other than the people who review those data. Toxicologists such as myself make it, pathologists

[840]

and so on. There is -- I don't know if I am explaining this correctly.

First of all, these studies that were done, say, by Merrell are submitted to the Food and Drug Administration to present their view, right, this is the documentation of their view that the drug that they make is safe for humans, not for rats, rabbits and so on. That is the purpose that they are doing such tests. Bendectin is not sold to animals. The reviewers in the FDA, again, toxicologists, pathologists such as myself, they all have the human animal as a point of reference and concern. That is why we are working there.

THE COURT: When all of the information is put together, the person in which position makes the final decision as to whether or not it is safe for human being or unsafe?

THE WITNESS: I cannot answer what person, but I can--

THE COURT: What position?

THE WITNESS: What position or rather what discipline goes to that.

THE COURT: No, the final analysis. Who finally says that is okay or this is not okay. To whom does that fall?

* * *

8. Excerpts of testimony of James W. Newberne, D.V.M., in *Ealy v. Richardson-Merrell, Inc.* (Ex. 27 to Pltfs.' Opp. to Summ. Judg.), filed Aug. 22, 1989

UNITED STATES DISTRICT COURT
For the District of Columbia

NO. 83-3504

Sekou Ealy, et al.,

Plaintiffs,

v.

Richardson-Merrell, Inc.,

Defendants.

June 30, 1987
Courtroom 7
Washington, D.C.

The above-entitled matter came on for trial before the Honorable June L. Green at 10:05 a.m.

Reported by: Bonnie L. Cahagan

Dawn Copeland
Official Reporter
Phone (202) 535-3397
3rd and Constitution Avenue, N.W.
Washington, D.C. 20001

[2506]

THE COURT: All set

MR. AUSTRIAN: Thank you your honor. At this time the defendant would call Dr. James Newbern to the stand.

JAMES W. NEWBERNE,
a witness, called for examination, having been first duly sworn, was examined and testified as follows:

DIRECT EXAMINATION
BY MR. AUSTRIAN:

Q. Good morning Dr. Newberne.

A. Good morning.

Q. Dr. Newberne, are you presently employed by Merrell Dow Pharmaceuticals?

A. Yes, sir.

Q. What is your present position?

A. My present position is vice-president of drug safety assessment.

Q. Are you a veterinarian?

A. Yes, sir.

Q. Are you a pathologist, veterinary pathologist?

A. Yes, sir.

Q. Can you tell me whether during the period

* * *

[2678]

makeup of the organism is important. That is essentially what he said, and that it does react to the environment and to the events around it.

Q. What he is saying is that in an animal that different animals may have different degrees of susceptibility depending on their makeup, isn't that right?

A. That is true.

Q. Of course, that also applies to man, doesn't it?

A. It is my understanding that it does, yes.

Q. Okay. Now, doctor, he goes on and gives on the next page the second principle, where he says:

"Susceptibility to teratogenic agents varies with the developmental stage at the time of exposure."

I read that right, didn't I?

A. Yes, sir.

Q. What he means by that is whether or not the animal is going to be susceptible to being affected by the teratogenic agent depends on whether or not the agent is present at the time that a portion of the body is developing; isn't that right?

A. That is my understanding.

Q. Timing is important?

[2679]

A. Timing, yes.

Q. Okay.

Then if we go back to page 54, it says number 3, "Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis)."

Did I read that right?

A. Yes.

Q. What that means is that the teratogens do something to affect the way the cells are developing to cause it, abnormal development; is that basically right?

A. In the context of this entire chapter, as I understand it, your comments are correct. What Dr. Wilson is referring to here is the developing cells and tissues in the complete animal.

Q. Sure. Again, both number 2 and I referred to and number 3, the timing question, and the mechanisms, that applies to humans as well as to the other animal species; isn't that right?

A. I think that is correct.

Q. We are all animals of some sort; that is right?

A. That is right.

Q. Okay.

* * *

[2698]

animals at a human dose, you would have to test thousands of animals in order to find out if there is a relationship between the drug and the teratogenic effect?

A. Early on in consideration of a study I don't give any consideration myself and I think this is true among most teratologists that one should even consider the human dose in that context. One should first consider what high doses, low doses or any other kind of dose is doing to that particular animal, and from the data derived from that animal, make a judgment of predictive value in human beings.

Q. To you, sir, last -- I believe it was April or May of 1986. The question is at page 61.

"Doctor, it is true that high doses are used in animal tests purposely, there is a purpose in use for selecting high doses, correct?

"Answer: That is a school of thought.

"Question: Do you agree with that school of thought?

"Answer: In a general sense I agree with it.

"Question: If we tested drugs at the human dose, you would have to test hundreds or thousands of animals, correct?

* * *

9. Affidavit of Shanna Helen Swan, Ph.D and curriculum vitae (Dock. No. 187), and excerpts of testimony in *Ealy v. Richardson-Merrell, Inc.* (Ex. 12 to Pltfs.' Opp. to Summ. Judg.), filed Aug. 22, 1989, and Sept. 28, 1989

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UNITED STATES DISTRICT COURT
For the Southern District of California

NO. 84-2013-G(I)

WILLIAM DAUBERT and JOYCE DAUBERT, Individually and as Guardian[s] Ad Litem for JASON DAUBERT, a Minor,
Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES 1 through 50 Inclusive,
Defendants.

NO. 84-2929-G(I)

MICHAEL SCHULLER, ANITA DE YOUNG, and ANITA DE YOUNG as Guardian ad Litem for ERIC SCHULLER,
Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES 1 through 50., Inclusive
Defendants.

AFFIDAVIT OF SHANNA HELEN SWAN

1. My name is Shanna Helen Swan.

2. I am an epidemiologist and biostatistician. I have a PhD in statistics. I practice in the field of reproductive epidemiology full time for the State of California. A copy of my curriculum vitae is attached hereto.

I was graduated from the City College of New York with my major in mathematics. I received a masters in biostatistics from Columbia University and then receive a PhD in statistics from the University of California at Berkeley. I have taught at the University of California. My teaching has involved the areas of statistics, biostatistics, epidemiology, and mathematics. Mathematics is the foundation for each of biostatistics and epidemiology. It is necessary that one have an understanding of statistics in order to teach epidemiology and to understand the meaning of epidemiology findings. I hold a [lecturer] position in epidemiology in the School of Public Health at the University [of] California at Berk[e]ley.

My current title is Chief of the Reproductive and Epidemiological Program of the Epidemiological Study Section of the California Department of Health and Services. My duties include the study of causes of adverse reproductive outcomes.

I have served as a consultant to the World Health Organization, to the Food and Drug Administration, and to the

National Institutes of Health. I belong to numerous professional societies that deal with epidemiology and statistics including the American College of Epidemiology, the American Statistical Association, the Society for Epidemiological Research, the Institute of Mathematics Statistics, the Biometrics Society and the American Public Health Association. I am a member of the Phi Beta Kappa Society. I have served as a reviewer for the epidemiological, statistical and medical publications including the American Journal of Epidemiology, American Journal of Public Health, The American Statistical Association, the Journal of the American Medical Association and others. I have served on study sections for the National Institutes of Health. I have published approximately 25 to 30 times in the field of epidemiology, biostatistics and statistics including an abstract with respect of Bendectin. I have co-authored numerous government documents from the state of California including those pertaining to pregnancy and pregnancy outcomes.

3. In my position with the state of California I am called upon to help determine causes of adverse pregnancy outcomes including birth defects where we utilize primary and secondary data. The type of data that I utilize and will be discussing below is all of the type of data that is generally and reasonably relied upon by epidemiologists to help determine whether o[r] not there is a statistical association

[4]

between a drug, such as Bendectin, and a class of birth defects such as limb reductions.

4. I have reviewed, to the best of my knowledge, all the epidemiological literature pertaining to Bendectin.

5. Because of my position, experience, education, and training I am aware that in vitro studies, animal studies and the pharmacology of drugs are all important along with epidemiology studies in determining whether or not there is a cause and effect relationship between drug and a birth defect. Decisions concerning whether or not there is such a cause and effect relationship between a drug and birth defects are not made solely on epidemiological data when one is concerned about teratogenicity issues. One would not rely solely on epidemiological studies that failed to show a statistical association at the 95% confidence level between a substance and a defect to determine that the substance does not cause the defect.

6. In order to understand epidemiology studies one must understand that the results can be positive, negative, or inconclusive. An inconclusive study is one that does reach traditional levels of statistical significance but does not have the statistical power to rule out appreciable relative risks. In other words, the data could be consistent both with no effect and with an effect that one was worried about such as a doubling of risks. A positive study at a traditional level of statistical significance, e.g. 5% would enable one to

[5]

conclude with 95% certainty that there is statistical association between a cause and effect or between a drug and a birth defect. In analyzing the validity of an epidemiological study one must analyze not only the chance of the error of a false positive, e.g.5%, but also the "power" of the study, the chance of detecting an association if it exists. A confidence interval indicates that the true association level is somewhere in the range between the lower limit an the higher limit of probability. The less sure one wants to be about the finding, the narrower is this range. For example for a 90% confidence level, the range would be narrower than for a 95% level and even narrower for an 85% confidence level and so on. It is erroneous to conclude that merely because a confidence interval includes the number 1.0 that one can conclude from such data that there is no statistical association or no causation. One must look at all the studies and evaluate their quality and power using one's education, training, and experience and generally accepted methodology to come to an opinion as to whether or not the data shows an association.

7. It is not usual epidemiological practice for the author of a study to "conclude" that the data does or does not "prove" a cause and effect relationship. That is neither the nature nor purpose of such a study or studies. The purpose of such data collection is to add another body of data to other scientific data such as pharmacological data, animal studies

[6]

data, and in vitro data to enable one to reach an opinion concerning the effect of the agent.

8. For example, in reviewing the various epidemiological studies on Bendectin, the most powerful study, i.e. "Jick", only has

approximately a 17.6% chance of finding a doubling of the rate of defects. The other studies are even less apt to find even a doubling. Even if one were to put all the studies together that involve the limbs, there would still be less than a 50% chance of finding a doubling of increased limb defects and only a minuscule chance of finding 50% increase or a 20% increase. In analyzing the various epidemiology studies, one quickly can see that the studies either have insufficient numbers, inappropriate control groups, inappropriate pooling of malformations, misclassification of exposure, or confounders.

9. It is not accepted epidemiological practice to rely solely on epidemiological studies that provide relative risks with confidence intervals which include 1.0 and conclude that Bendectin does not cause birth defects. Such studies may in fact provide data consistent with a greatly increased risk.

10. Having reviewed the epidemiological studies including, but not limited to Heinonen, Jick, Aselton, Morelock, Cordero, Eskenazi, McCredie, and based upon generally accepted epidemiological techniques and utilizing my education, training and experience it is my opinion that one cannot conclude that there is in fact no statistical

[7]

association between Bendectin an limb reduction defects. More specifically one cannot draw a conclusion from those studies that Bendectin does not cause limb reduction defects.

11. Because limb defects are a rare occurrence, occurring less than one per one thousand live births, many thousands of births would be necessary in a controlled study to reveal even a 100% increase. The chances of finding a smaller increase such as a 10% or 20% would therefore be minuscule. That is one reason why an epidemiologist would not rely only on epidemiology studies in the face of other scientific data to suggest that a drug, such as Bendectin, does not cause birth defects. On the contrary, the prudent epidemiologist would be concerned about the public safety and when there is data consistent with increased risks, as with Bendectin, conclude that it is more probable than not that Bendectin is associated with birth defects.

12. Rather, considering the foregoing studies, within a reasonable degree of certainty, based upon my education, training

and experience, it is my opinion that considering all available data that is provided in animal, in vitro and epidemiological studies, including the relative risks, the confidence limits and also the power of the studies, that it is more likely than not that Bendectin is, in fact, associated with limb reduction defects. in reaching that opinion, I have used the methodology that is generally and reasonably relied upon by epidemiologists to analyze, study and interpret data

[8]

that has been collected, published and unpublished in trying to draw opinions concerning whether or not there is a cause and effect relationship between a drug and a birth defect.

13. I have previously given testimony in cases involving Bendectin and subsequently learned that the defendant in these cases has taken bits and pieces of my testimony out of context. However, so there be no question, it is my opinion within a reasonable degree of certainty, based on all of the available data, the Bendectin is associated with birth defects, including limb defects.

/s/
Shanna Helen Swan

Sworn to and subscribed in my presence on this 27th day of September 1989.
State of California
County of Alameda

/s/
Notary Public

CURRICULUM VITAE

Shanna Helen Swan
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EDUCATION

1963 — DOCTOR OF PHILOSOPHY
Department of Statistics
University of California, Berkeley

Dissertation Topic:
Limiting Distributions of Random Sums of Independent Random Variables [see publication (1)]

1960 — MASTER OF SCIENCE
Department of Biostatistics,
Columbia University, New York
Regents Teaching Fellow

1958 — BACHELOR OF SCIENCE (Mathematics; Magna Cum Laude) City College of New York, New York Honors in Logic (Ward Medal)

NONACADEMIC EXPERIENCE

1981 to present — CHIEF
Health Assessment and Surveillance Unit
Epidemiologic Studies and Surveillance Section
California Department of Health Services-
Berkeley, California

Directing and carrying out research on reproductive effects of toxic substances, providing consultation staff on the design and analysis of epidemiologic projects, supervision of unit staff.

1969 to 1978 — SENIOR BIOSTATISTICIAN
Contraceptive Drug Study Kaiser Permanente
Medical Center Walnut Creek, California

Directed and carried out research on noncontraceptive side effects of oral contraceptives." Designed and supervised study of cervical carcinoma, oral contraceptive use and sexual behavior, developed grant proposal for study of vasectomy and cervical carcinoma [see publications (11) through (22)].

1972 — CONSULTANT IN CONTRACEPTIVE RESEARCH
World Health Organization
Bangkok, Thailand

1971 — RESEARCH ASSOCIATE
Berkeley Pediatric Group
Berkeley, California

Designed and analyzed study on tetracyclines and tooth color in children [see publication (10)].

1964 to 1967 — RESEARCH SEISMOLOGIST
Department of Seismology
University of California, Berkeley

Analyzed seismological data on travel times of P waves; designed and supervised study on reliability of reading of seismograms collaborated with international committee on revision of travel time standard tables [see publications (2) through (9)]

ACADEMIC EXPERIENCE

1980 to present — LECTURER IN BIOSTATISTICS AND EPIDEMIOLOGY
School of Public Health
University of California, Berkeley

Responsibilities include: teaching biostatistical and epidemiologic methods, supervision of graduate research.

1979 to 1981 — DIRECTOR
Graduate Training Program in Biostatistics and Epidemiology
School of Public Health
University of California, Berkeley

Responsibilities included: supervision of graduate research projects, supervision of field placements, maintenance of data archives, lecturing in biostatistics and epidemiology.

1978 to 1979 — VISITING ASSOCIATE PROFESSOR
Department of Statistics. Chairman: Peter Bickel
University of California, Berkeley

Responsibilities included: teaching both introductory probability and statistics, supervision of Teaching Assistants and Readers.

1973 to 1979 — ASSOCIATE PROFESSOR
Department of Mathematics. Chairman: Robert Johnson
State University of Sonoma, Rohnert Park, California
Responsibilities included: teaching introductory and advanced probability and statistics, development of interdisciplinary courses; supervision of Masters students.

1968 to 1969 — LECTURER
Department of Biostatistics. Chairman: Jacob Yerushalmy
University of California, Berkeley

Responsibilities included: teaching of introductory biostatistics.

1967 to 1968 — LECTURER
Department of Statistics. Chairman: Joseph Yahav
University of Tel Aviv, Israel

Responsibilities included: teaching applied statistics, supervisor of student research.

1963 to 1964 — ASSISTANT PROFESSOR
Department of Statistics. Chairman: Lucient le Cam
University of California

Responsibilities included: teaching introductory probability and statistics[.]

1960 to 1961 LECTURER
Department of Statistics. Chairman: Anders Hald
University of Copenhagen, Copenhagen, Denmark

Responsibilities included: teaching introductory and graduate seminar in probability theory.

PROFESSIONAL SOCIETIES

Phi Beta Kappa
American Public Health Association
Biometric Society
Institute of Mathematical Statistics
Society for Epidemiologic Research
American Statistical Association
American College of Epidemiology

REVIEWER

Journal of the American Statistical Association
American Journal of Epidemiology
Journal of the American Public Health Association
Journal of the American Medical Association

COMMITTEE MEMBER

American Statistisal Association Committee on Law and Justic Statistics

STUDIES SECTION MEMBER

Health Services Developmental Grants Review Subcommittee, National Center for Health Services Research (1986-1988).

SPECIAL STUDIES SECTION MEMBER

Contraceptive Evaluation Branch, National Institutes of Health,
Child Health and Development Branch, National Institutes of Health,
Oral Contraceptive Review, FDA

PUBLICATIONS

(1) Freedman, H.*: Limiting distributions of random sums of independent random variables. Z. Wahrscheinlichkeitstheorie 3:7-18, 1964.
(2) Freedman, H.*: The "little variable factor," a statistical discussion of the reading of seismograms. Bulletin of the Seismological Society of America (B.S.S.A.) 65 (2): 593-604, 1966.
(3) Freedman, H.*: A statistical discussion of Pn residuals from explosions. B.S.S.A. 65(3): 677-695, 1966.
(4) Freedman, H.*: On estimating the accuracy of source "parameters." B.S.S.A. 1967.
(5) Freedman, H.*: A statistical discussion of Pn residuals from explosions Part II. B.S.S.A. 1967.
(6) Freedman, H.*: On estimating earthquake magnitude. B.S.S.A. 1967.
(7) Freedman, H.*: Seismological measurement and measurement error. B.S.S.A. 58-4, 1968.
(8) Freedman, H.*: Group analysis of variance for earthquake location and magnitude, (with Bruce Bolt). Nature 217:5223, 1968.

(9) Freedman, H.*: Seismological tables for P phases (with Herrin, et al.). B.S.S.A. 58: 1, 1968.
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(11) Fisch, I.R., Freedman, S.H.* and Myatt, A.V.: Oral contraceptives, pregnancy, and blood pressure. J.A.M.A. 222(12): 1507-1510, December 18, 1972.
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(14) Fisch, I.R., Freedman, S.H.*: Oral contraceptives and the red blood cell. Clin. Pharmacol. Ther. 14(2): 245-249, March-April 1973.
(15) Freedman, S.H.* and Anderson, N.E.: Spirometry and oral contraceptives. Am. J. Obstet. Gynecol. 116(5): 682-688, July 1, 1973
(16) Fisch, I.R., Freedman, S.H.*: Oral contraceptives, ABO blood groups, and in vitro fibrin formation. Obstet. Gynecol. 46*4): 473-479, Oct. 1975.
(17) Fisch, I.R., Freedman, S.H.*: Smoking, oral contraceptives, and obesity. Effects on white blood cell count. J.A.M.A. 234(5): 500-506, Nov. 3, 1975.
(18) Freedman, S.H.* and Fisch, I.R.: Automated multitest laboratory phases and quality control procedures. In: S. Ramcharan (ed.), The Walnut Creek Contraceptive Drug Study, vol. 1. DHEW Publ. No. (NIH) 74-562.
(19) Freedman, S.H.* and Fisch, I.R.: Oral contraceptives, pregnancy and the leukocyte count. In: S. Ramcharan (ed.), The Walnut Creek Contraceptive Drug Study, vol. 2.
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UNITED STATES DISTRICT COURT
For the District of Columbia

NO. 83-3504

Sekou Ealy, et al.,

Plaintiffs,

v.

Richardson-Merrell, Inc.,

Defendants.

July 8, 1987
Courtroom 7
Washington, D.C.

The above-entitled matter came on for trial before the Honorable June L. Green at 10:00 a.m.

Reported by: Bonnie L. Gahagan

Dawn Copeland
Official Reporter
Phone (202) 535-3397
Room 4806-B, U.S. Courthouse
3rd and Constitution Avenue, N.W.
Washington, D.C. 20001

[3523]
MR. NACE: Call our witness?
THE COURT: Okay.
(In open court.)
MR. NACE: Your Honor, we are going to call Dr. Shanna Swan as our witness, as soon as she comes in.

Whereupon --

SHANNA HELEN SWAN,

a witness, called for examination, having been first duly sworn, was examined and testified as follows:

DIRECT EXAMINATION

BY MR. NACE:

Q. Doctor, give us your full name, please.
A. Shanna Helen Swan
Q. S W A N?
A. S W A N.
Q. I just said doctor. Are you a medical doctor?
A. I am not.
Q. You are an epidemiologist?
A. And biostatistician.
Q. Do you have a Ph.D.?
A. In statistics.
Q. Before I get to that, I just want to ask you, do you treat patients?

[3524]

A. No.
Q. Do you go to nursing homes one or two days a week to treat patients?
A. No.
Q. Do you practice in a field of reproductive epidemiology?
A. I do.
Q. Full time?
A. Yes.
Q. For whom?
A. I work for the State of California and I study -- well,

I am in charge of a large unit whose job it is to study the effects of environmental pollution on women's reproductive health; that is, their risk of spontaneous abortions, birth defects and other adverse pregnancy outcomes.

Q. Is that your full-time occupation?
A. It is.
Q. Do you consult with either drug companies or plaintiffs' attorneys two or three days a week?
A. No.
Q. Okay.
A. Although I do consult.
Q. You do consult?
A. Yes.

[3525]

Q. Let me ask you a little bit about your education. Where did you go to college?
A. I graduated from the City College of New York in mathematics.
Q. Where -- did you do additional training?
A. I did. I got a Master's in biostatistics from Columbia University.
Q. In New York?
A. In New York.
And then I got a Ph.D. in statistics at the University of California at Berkeley.
Q. Is that a Ph.D. where you worked with statistics? Is that right?
A. It was actually theoretical statistics.
Q. Is a Ph.D. given in what is called theoretical statistics.
A. Right.
Q. Do you have a Ph.D. in philosophy?
A. Doctor of Philosophy it is called.
Q. Doctor of Philosophy?
A. Yes.
Q. How does that relate to the Ph.D. that you told us about in theoretical statistics?
A. That is a the degree, Doctor of Philosophy in statistics.

[3526]

Q. I have to ask, when you got your Ph.D., did you have to do a particular thesis on a particular topic?

A. Yes.

Q. Could you tell us what your topic was?

A. Well, it was a topic in abstract probability theory and it was called the limiting distribution of random sums of independent rand variables.

Don't ask me to explain.

Q. I won't. About when did you get your Ph.D. in the statistics area?

A. In 1963.

Q. After you got your Ph.D. in statistics, did you become involved in the world of academics?

A. Yes, I did.

Q. As a professor eventually?

A. The highest academic degree I held was associate professor.

Q. Where did you teach?

A. I taught at the University of California at Berkeley, California State University, Sonoma, and also for two one-year stints, if you will, at the University of Copenhagen in Denmark and the University of Tel Aviv in Israel.

[3527]

Q. What subjects were you teaching?

A. I taught areas of statistics, biostatistics, epidemiology, mathematics.

Q. What is the relationship between biostatistics and epidemiology and mathematics?

A. Mathematics is the foundation, if you will, for all of those sciences as it is for physics or chemistry, so that is kind of the ground, and then on top of that is the theory of statistics which deals with random phenomena, things that are not certain. In particular -- that could be batting averages or cars, but it also could be health, and if you go into health and biology with statistics, that is biostatistics, and then if you want to design and carry out studies to address questions of causes of disease, that is epidemiology.

So, if you will, it is kind of a pyramid.

Q. They are all interrelated, then, in some fashion?

A. Yes, they are.

Q. So you need an understanding of statistics in order to teach epidemiology?

A. Absolutely.

Q. And to understand the meaning of epidemiology findings?

[3528]

A. Yes.

Q. Up until what year roughly were you involved in teaching?

A. I am still, although -- I am now an adjunct lecturer, unpaid lecturer, at the University of California, and that is for the technical reason that I work for the state and University of California is a state school, so I cannot be paid twice by the state, so the Department of Health gives me what is called release time, allows me to use some of my time that they pay me for to go over [to] the campus and teach.

Q. What do you teach?

A. I teach in the School of Public Health in the graduate program and I teach biostatistics and epidemiology.

I should add that I am doing that less and less as my work at the state gets more and more demanding, so probably this year I will just do, I don't know, six, eight lectures, something like that.

Q. In a school year?

A. Right.

Q. Let's --

A. Excuse me, and I also have Ph.D. students.

Q. You have Ph.D. Students?

[3529]

A. Students who are getting their Ph.D. theses under my supervision.

Q. I see. They will be getting their Ph.D.'s in statistics and biostatistics or something like that, that area?

A. Mostly epidemiology, but some biostatistics or some jointly biostatistics and epidemiology.

Q. Currently, then, what is your actual title and where do you work?

A. My title is chief of the health assessment and

surveillance unit, it is a long one, of the epidemiological studies and surveillance section of the California Department of Health Services.

Q. What do you do there?

A. What I do there is study reproductive health, particularly -- well, spontaneous abortions and birth defects in relation to exposures in the air and in the water, but also in general causes of adverse reproductive outcomes.

Q. Does this deal, then, with exogenous substances?

A. Yes.

Q. I think we have heard about exogenous substances before.

[3530]

Since about when have you been chief?

A. Around January -- well, the end of '81, I believe.

Q. Prior to that time, what did you do?

A. Well, I only joined the state in September of '81, and the first few months I wasn't unit chief, I was biostatistician, and then I was made unit chief, but before that I was the head of the graduate training program in the School of Public Health in biostatistics and epidemiology.

Q. Have you served as a senior biostatistician?

A. Yes.

Q. What is a senior biostatistician and where did you serve?

A. A senior biostatistician is simply the top, you know, a top biostatistician on a project as opposed to more junior biostatistician and I worked with a large study, a study of oral contraceptives and their noncontraceptive side effects in a large cohort of women in Kaiser, which is a prepaid health plan in California.

Q. Have you also been a consultant in that area?

A. Yes, I have.

[3531]

Q. To whom?

A. I have been a consultant to the World Health Organization, to the Food and Drug Administration, to the National Institutes of Health, and that is all.

Q. When you were with the World Health Organization

as a consultant, where were you located?

A. In Bangkok.

Q. Thailand?

A. Yes, that was just a short consultation.

Q. Doctor, do you belong to some professional societies that deal with epidemiology and biostatistics?

A. Yes.

Q. Let me just ask you about a few of them. Do you belong to the American College of Epidemiology?

A. Yes.

Q. What is that?

A. It is a professional society that you are elected to.

Q. Who belongs to that generally?

A. Epidemiologists.

Q. Do you belong to the American Statistical Association?

[3532]

A. I do.

Q. Do you belong to the Society for Epidemiological Research?

A. I do.

Q. What is that?

A. That is another professional epidemiology society.

Q. Do you belong to the American Association for the Advancement of Science?

A. Not any more.

Q. Not any more?

A. No, got too expensive.

Q. How about the Institute of Mathematics Statistics?

A. I do.

Q. How about the Biometrics Society?

A. Yes.

Q. What is a Biometric Society?

A. Well, biometrics is another name for biostatistics, is it is a biostatistical organization.

Q. Do you still belong to the American Public Health Association?

A. Oh, yes.

Q. How about the Phi Beta Kappa?

[3533]

A. Yes.

Q. What is Phi Beta Kappa?

A. It is an honor society that you are elected to if you grades are high enough.

Q. In School?

A. Yes.

Q. Have you served as a reviewer for any epidemiological publications?

A. Yes.

Q. Which ones?

A. The American Journal of Epidemiology and epidemiological reviewer for American [J]ournal of Public Health, and I am a reviewer for some medical journals as well.

Q. Have you reviewed for the American Statistical Association, their journal?

A. Yes.

Q. Are you a member of any committees that deal with statistics?

A. Yes.

Q. What would that be?

A. I am a member of the committee of the American Statistical Association called the law and justice committee, and also I serve on various study sections for the National Institute of Health.

[3534]

Q. What is a study section?

A. A study section is a group of people who are appointed to serve for three or four years to review applications for funding for research so scientists send in their grant or contract applications and this committee meets three times a year here in Bethesda actually to decide who should get money.

Q. That is for NIH?

A. Actually, my study section is with the National Center for Health Services Research, and I have also been on special study sections for the National Institutes of Health. Those are study sections around a particular problem rather than meeting over a period like three or four years.

Q. Have you published in the field of epidemiology and

biostatistics and statistics?

A. Yes, I have.

Q. Approximately how many times?

A. 20, 25. I have a couple of more recent articles.

Q. Okay. Could you just tell us some of the areas that you have published in that might be somehow involved with reproductive health or reproductive epidemiology?

[3535]

A. Actually I just gave a paper on the effects of a chemical exposure in cooking oil and did a critique of a paper in Taiwan which caused birth defects in children. I gave a paper, also, last month, invited paper on the future of environmental epidemiology, basically, future directions for environmental epidemiology.

I did a large paper report which is now coming out as a -- in a journal on spontaneous abortion and birth defects in connection with contaminated drinking water in a south base community, Silicon Valley, where they make chips.

Q. Computer chips?

A. Computer chips

I had a paper on tetracycline and children's teeth.

Q. You said you were invited to give a paper. I think that was basically your language. What does it mean when you are invited to give a paper?

A. Well, whoever is planning a session feels that you are an expert and they want you to talk about the subject.

Q. You have been asked to do that at epidemiological gatherings?

A. Yes.

[3536]

Q. Doctor, have you co-authored or authored any government documents that pertain to pregnancy and pregnancy outcomes?

A. Yes.

Q. For which government?

A. This State of California.

Q. Did you actually publish an abstract with respect to Bendectin?

A. I published an abstract and I presented two papers.

Q. Okay. Now, when you say you presented two papers, would you explain to us how that comes about, who you present them to and what it means when you present papers?

A. Well, one of these was for the Society of Epidemiological Research. That is the organization you asked me about before, and in February there is a collar for abstract, if you want to give a paper, beginning of June you send in your abstracts and your abstracts are reviewed by epidemiologists. They select, I would say, 10 to 15 percent of those submitted. I am guessing at the number, but it is getting very difficult to get an abstract accepted. And then you are asked -- you are assigned a session to present your paper at.

[3537]

That is generally the same procedure that you go through for the other organization, the American Public Health Association which presents -- has a meeting in October, so you send you abstract in and reviewed and then it gets selected and then you present your paper.

Q. Before you have an abstract published, is there "a peer-reviewing process" that it goes through?

A. Definitely.

Q. That peer-reviewing process is what?

A. The review and selection of your abstract for the meeting, and if you pass that review, then because you were given at the meeting, you will have your abstract published.

Q. Doctor, we have heard names in this courtroom. Kenneth Rothman. Do you know Dr. Rothman?

A. I do.

Q. Do you know Dr. Jose Cordero? Do you know him?

A. Yes.

Q. We have heard the name Brenda Eskanazi. Do you know Brenda Eskanazi?

A. Yes, I do.

[3538]

Q. Is that Dr. Eskanazi?

A. Yes.

Q. Allen Mitchell, Dr. Allen Mitchell. Do you know him?

A. Yes, I do.

MR. NACE: I would offer Dr. Swan as an expert in the field of epidemiology and biostatistics.

THE COURT: Questions?

EXAMINATION ON THE VOIR DIRE

BY MR. AUSTRIAN:

Q. Good afternoon, doctor.

A. Hello.

Q. As I understand it, you are not a medical doctor, is that correct?

A. That is right.

Q. You have no medical training or medical license?

A. Correct.

Q. When it comes to diagnosing or treating or caring for patients, you have no hands-on experience; is that true?

A. Right.

Q. Your degree is in mathematics and statistics, correct?

[3539]

A. Right

Q. You are not a teratologist or pharmacologist?

A. Correct.

Q. And you have no expertise in the field of toxicology?

A. Correct.

Q. Toxicology is a study of the effects of drugs on humans; is that true?

A. Yes, but I also study the effects of drugs on humans.

Q. I understand that, but you are not a toxicologist?

A. I am not a toxicologist.

Q. Now, you have never collected data, set up a protocol and carried out an epidemiological study on Bendectin, have you?

A. Not on Bendectin.

Q. You have never done a cohort study on Bendectin, have you?

A. No.

Q. You have never done a case control study on Bendectin, have you?

A. Correct.

Q. Is that true?

[3540]

A. True.

Q. What you have done is reanalyze data by a governmental data base, the Center for Disease Control; isn't that correct?

A. I have done that and I have also done an analysis of the literature on Bendectin.

Q. I understand, but in terms of the abstract that you mentioned earlier, this was a reanalysis of data done by the United States Center for Disease Control?

A. Correct.

Q. And that is the Center for Disease Control is a governmental agency, federal agency; is that correct?

A. Yes, yes.

Q. Now, when you did your reanalysis, you were not employed by the CDC, or Center for Disease Control, were you?

A. No.

Q. That reanalysis which resulted in the abstract was not in any way sponsored by the federal government, was it?

A. No.

Q. In fact, the reanalysis that you did was funded by plaintiffs' lawyers suing Merrell Dow;

[3541]

isn't that correct?

A. That is correct and I should add that I so stated both times I presented the paper.

Q. In fact, when you presented your paper, you said you have a bias because the reanalysis of data that you did was funded by a plaintiffs' lawyer; isn't that correct?

A. That is not correct. What I said, and what I believe is correct for people who are paid by interested parties to do is to make the audience aware of the funding source because of the potential for bias.

Q. The fact that you were funded by plaintiffs' law firm does not appear in the abstract that you published; isn't that correct?

A. That is correct.

Q. The funding was approximately $15,000 by the plaintiffs' law firm for your reanalysis; isn't that correct?

A. I don't recall. That sounds about right.

Q. That $15,000 does not include statements that you

have sent to plaintiffs' counsel for assisting in giving testimony, does it?

A. I don't recall.

Q. Now, in fact, for about one year prior to

[3542]

July of 1984 you were spending at least one day a week consulting with lawyers; isn't that correct?

A. I don't recall.

Q. Would it be fair to say that in terms of the reanalysis that you did, it was only because of the litigation that made that possible?

A. It would have been possible for me to get the data base had I had a lot of money, but it is expensive.

Q. I understand.

Now, can you tell me whether after you received or did your reanalysis you wrote up a report of your study?

MR. NACE: I don't mind him asking these questions, but I don't believe on voir dire it is proper.

MR. AUSTRIAN: He asked questions in terms of the abstract and I am entitled, I think, to ask whether she ever wrote up the results of her study?

MR. NACE: I just don't believe it is proper voir dire.

THE COURT: Overruled. Go ahead.

BY MR. AUSTRIAN:

Q. Did you ever write up your results of your study?

[3543]

A. No, I have not yet.

Q. Did you ever submit your study to a peer-review journal to be published?

A. I have not yet, but I would like to also add that I also have not yet submitted the results of the study I did for the state, two studies I did for the state. It is just -- I don't have time.

Q. You started your analysis, did you not, in 1982?

A. That is correct, and I started the Fairchild study in 1982, also, and that is not published and that was certainly something I was paid for by the state.

Q. In terms of the people who assisted you with the reanalysis, is it also true that some of them were employees of

the plaintiffs' law firm?

A. I would say probably 2 or 3 percent of the work was done by employees by the plaintiffs' law firm at the beginning and then I took that data myself away from that law firm.

Q. Now, the data that you did the reanalysis had nothing to do with your employment at the State of California, did it?

A. No.

Q. You have been involved in at least 23

[3544]

cases involving actions against pharmaceutical companies, have you not?

A. I don't know.

Q. Would that be a fair statement?

A. I don't recall.

Q. When you first began your reanalysis, you had no written protocol for that study, did you?

A. CDC had a written protocol.

Q. You did not have a written protocol for that study, did you, doctor?

A. The answer is no, but I would like to explain. There are -- it is not appropriate to have a protocol for a reanalysis of an existing data base. This is done all the time.

For example, Dr. Mitchell continually goes back and reanalyzes his data, Dr. Cordero does that and we do that in the state, and every time you do a reanalysis, you don't write another protocol. It is not done.

Q. When you reanalyzed the data for the CDC, you used a different definition for the first trimester, different definition of the items to be used in the study and different definition for controls?

A. Those were written down specifically.

Q. Those were not written down before the

[3545]

study was --

A. Yes, they were.

Q. You started you reanalysis before the CDC was published in the Journal of the American Medical Association in 1980?

A. No, before my reanalysis was published.

Q. Your reanalysis has never been published in a peer-review journal, is that correct?

A. The abstract was.

Q. No, your reanalysis and the discussion of the data has never been --

A. I said that, but you asked me whether the definitions were written down before my results were published and I said yes.

Q. Your results have never been published in a peer-review journal?

A. An abstract of them have been published, a paper on it has not been published. We can talk about abstract and paper.

Q. Just so we are clear, I am talking about paper, a paper.

A. No, a paper has not been published.

Q. You have never written up the study or paper so that someone can actually look at and consider how you actually arrived at your data,

[3546]

isn't that also true?

A. That is true, although I did discuss it on many occasions with Dr. Cordero and with a number of my colleagues both privately and at those two meetings, so certainly in the epidemiological view.

Q. There is no place in medical literature where you have put together a report describing your reanalysis and how you got the figures and the definitions that you used; isn't that correct?

A. That is correct.

MR. AUSTRIAN: Nothing further.

May we approach, your Honor?

THE COURT: Yes.

(At the bench.)

MR. AUSTRIAN: I object to any testimony concerning the reanalysis of data, the Center of Disease Control data.

First, it is certainly not appropriate rebuttal to have a contention made that a study for reanalysis supports plaintiffs' case and should be done in the case in chief so that the defendant can in fact respond to it and not present it for the first time in the

rebuttal part of the case.

This witness could have been brought here

[3547]

in the case in chief and presented any data she had to suggest that Bendectin was associated with birth defects.

Secondly, in this testimony was not done independently, it was paid for by the plaintiffs' law firm, not Mr. Nace's law firm --

THE COURT: You said you would make that clear, but you haven't.

MR. AUSTRIAN: I will make that clear.

MR. NACE: I will.

MR. AUSTRIAN: I will make that clear.

THE COURT: I was disappointed.

MR. AUSTRIAN: I apologize, your Honor.

Furthermore, in terms of qualifications, she does not see children, deal with children. She is a statistician and certainly cannot give views on Bendectin's safety or lack of safety based on her background and training.

THE COURT: We have heard from so many people who haven't seen children and I don't think that would be a basis, would it?

MR. AUSTRIAN: Pardon?

THE COURT: I say we have heard from so many people who don't see children that I don't think that would be a basis, would it? Your

[3548]

objection is overruled.

(In open court.)

DIRECT EXAMINATION continued

BY MR. NACE:

Q. Doctor, I want to show you what has been marked a 438, a copy dated May 9, 1986 and I have crossed out that one section of American Association for whatever, and other than that, is that basically correct, up-to-date, except for a couple of more publications perhaps?

A. Yes.

Q. I want to ask you about the reanalysis that you were asked about. First of all, you indicated that you were funded or

it was paid for by some attorneys?

A. Yes.

Q. Was I or any member of my law firm one of those attorneys that paid for this?

A. No.

Q. I want to show you marked as Exhibit 504, and I think it is in the stack over here, I am showing you 504. Is that a copy of the reanalysis that you did as far as the abstract?

A. On page 486, the bottom right there is a copy of the abstract.

* * *

[3553]

Q. Doctor, in your field, in your position with the State of California, are you called upon to help determine the causes of birth defects?

A. Yes.

Q. What kind of data does an epidemiologist and a biostatistician use? And I don't want a 10-minute answer, just a short answer as to what kind of data do you utilize.

A. Two kinds. We utilize published data, where we pull together all the available information published. That is called secondary data collection or we do primary data collection where we go out an get new data through interviewing women, through medical records, birth certificates and so on.

Q. Now, do you yourself do in vitro studies or animal studies or work with pharmacology of drugs?

A. No.

Q. Are you aware of their relationships to determining whether or not a drug is a teratogen?

A. Yes.

Q. What is the relationship from the epidemiological standpoint?

A. We work with people in those fields in making the analysis of whether an observed

[3554]

statistical association is causal, and to do that we have employed, for example, in the state toxicologists, biochemists, animal

researchers and when we have a problem, we meet and talk about that and get everybody's input.

Q. Are decisions generally and usually made based solely on epidemiological data as to teratogenicity issues?

A. I am inclined to say never.

Q. Never?

A. Yes. I can't think of any situation where you would only rely on epidemiology. Maybe in an extreme example, but not in the course of my work.

Q. What do you mean by an extreme example? What are you talking about. I don't want a name of anything, but what do you mean by an extreme example?

A. Where the epidemiology was so impelling in and of itself that we would feel without taking the time to collect additional data, it was necessary to take an action in the interest of public health.

Q. Are decisions made that there is not an association between an exogenous substance such as a drug and a defect, are such decisions made solely on epidemiological data.

A. Again, I would have to say almost never,

* * *

[3575]

therapeutic principles and an article by Allen Mitchell. We have talked somewhat about the examples that he gives back on pages 68 and 69 regarding inconclusive positive and negative studies. To you as an epidemiologist, what is an inconclusive study?

A. An inconclusive study is one that doesn't reach traditional levels of statistical significance, but does not have the statistical power to rule out appreciable relative risks. In other words, the data could be consistent with either no effect or an effect that you were worried about.

Q. I believe Dr. Mitchell in the Yaffe book talks about on page 69 about two types of statistical analysis, a type 1 and a type 2 analysis and often a beta as he calls it.

A. Right.

Q. Are both of those analyses generally done when one is trying to determine the validity or to interpret an epidemiological study?

A. They should both be done.

Q. Why is that?

A. Because in any situation where you are doing research, you are using a sample, so you will run the risk of making a mistake. There are two

[3576]

kind of mistakes you can make. You can say that the drug is safe when it is not --

Q. Let me write something down here. Are we talking about type 1 and type 2?

A. Right.

Q. Let me do a type 1. Now, what is a type 1?

A. A type 1 is when you say that the drug is harmful when it is really safe.

Q. When you say harmful, and I will put that in quotes, when it is really safe?

A. Right, you do a study and you get a two, statistically significant, but just by the luck of the draw, it is really not an association and it is just bad luck.

Q. What is type 2?

A. The type 2 is to say that the drug is safe when it is really harmful.

Q. Safe when harmful?

A. So that would be when your study might have a relative risk which is smaller, 1.5 maybe, not statistically significant, you say the drug is safe, but in reality you miss something important.

Q. Are these types of errors?

A. These are errors, the two errors that you can make.

[3577]

Q. One is alpha and one is beta?

A. Alpha is type 1 and beta is type 2.

Q. This is an alpha sign?

A. Yes.

Q. This is a beta sign?

A. Yes.

Q. Now, when we talk about power, what does that apply to?

A. Power is just simply one minus beta.

Q. Is that a type 2 error?

A. Yes. The smaller the beta, the larger the power.

Q. Put power down here in the type 2?

A. However you want to write it, that is the fact. Power is one minus beta.

Q. One minus beta?

A. Right.

Q. What is the phrase that corresponds with the type 1 error, alpha error?

A. That corresponds to the confidence interval.

Q. Confidence interval. Okay. Now, the various studies that have been talked about, I believe, about the cohort, Jick, Aselton, Heinonen, Morelock --

[3578]

A. Yes.

Q. -- Jick, Aselton, Heinonen and Morelock, those studies, the way they are designed, are they more likely to show type 1 or type 2 errors?

A. None of them controls the type 2 error.

Q. What do you mean they don't control the type 2 error?

A. In all of those the type 2 error is very large. It is at least 80 percent.

Q. At least what?

A. 80 percent.

Q. Now, what does that mean?

A. That means that there is an 80 percent chance or greater that the drug could be harmful and these studies would conclude that it was safe.

Q. All right.

A. Where harmful means in this calculation a doubled risk of limb reduction defects.

Q. When we talked about a doubled risk of limb reduction defect --

A. 100 percent more of limb reduction defects of women who took Bendectin in the first trimester. That could be happening, in these studies probably 80 percent or greater would say the drug is safe.

Q. Now, with respect to the power to detect a

* * *

[3598]

A. Well, Jick has the most power.

Q. What are the chanees of the best one then, the Jick study, finding 100 percent increase?

A. 17 -- about 17 percent, 17.6.

Q. Would it be and accepted practice by epidemiologists to rely upon a study or even four studies, none of which had a power greater than 17 percent to detect 100 percent increase to decide that a drug is safe and could not cause birth defects?

A. No.

Q. Now, doctor --

A. Let me just say that these studies altogether if you had the power of all of these studies together --

Q. You mean by the numbers?

A. Yes, if somebody instead of doing four studies had done one study with all of these numbers, you would still have a power of less than 50 percent.

Q. Meaning less than 50 percent meaning there would be less than a 50 percent chance of finding 100 percent increase?

A. Yes.

Q. Putting them all together, if you have less than a 50 percent chance of finding 100 percent

* * *

10. Affidavit of Jay H. Glasser, Ph.D and curriculum vitae (Dock. No. 188), filed Sept. 28, 1989, excerpts of testimony in *Hill v. Merrell Dow Pharmaceuticals, Inc.* (Ex. 32 to Pltfs.' Opp. to Summ. Judg.), filed Aug. 22, 1989, and excerpts of deposition (Ex. J to Merrell Dow's Reply to Pltfs.' Opp. to Deft.'s Mot. for Summ. Judg.), filed Aug. 28, 1989

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UNITED STATES DISTRICT COURT
For the Southern District of California

NO. 84-2013-G(I)

WILLIAM DAUBERT and JOYCE DAUBERT, Individually and as Guardian Ad Litem for JASON DAUBERT, a Minor,
Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES 1 through 50 Inclusive,
Defendants.

NO. 84-2929-G(I)

MICHAEL SCHULLER, ANITA DE YOUNG, and ANITA DE YOUNG as Guardian ad Litem for ERIC SCHULLER,
Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES 1 through 50, Inclusive
Defendants.

[2] **AFFIDAVIT OF JAY H. GLASSER**

My name is Jay H. Glasser and I state as follows:

1. I have a Ph.D. in experimental statistics which I obtained after receiving my Bachelor's Degree from the University of Connecticut with a major in zoology and a minor in mathematics. Thereafter, I received a Master of Science in biostatistics from the School of Public Health at Columbia University, and then completed my formal education by receiving my Ph.D. and doing the necessary studies at the University of North Carolina and at North Carolina State University.

I am currently a professor of biometry and computer sciences and was the convener of the biometry module at the University of Texas, School of Public Health and am currently Co-Director of the Graduate Program for Health Technology Assessment.

Biometry is a study of and the design of studies dealing with the life sciences to evaluate medical experiments, population studies, to provide the machinery and methodology of such studies, primarily with application in the health fields, community health and public health. Biostatistics is the related aspect of biometry. Epidemiology is the study of the distribution of diseases in a population, both in time and space, with other modifiers, such as social conditions. Biometry and biostatistics are the fundamental contributors providing much of the mathematical background and the

[3]

theoretical background in the techniques that are used in epidemiology. Mathematics is the fundamental science; biostatistics

and biometry arise out of trying to apply analytic principles to study the life processes; and epidemiology involves looking at disease distributions.

My teaching experience has included teaching epidemiology, statistics, biometry, and biostatistics.

I have been a member of the Population Association of the Society for Epidemiological Research, of the American Statistical Association, The Royal Statistical Society, the American Public Health Association, various inter-American statistical associations, and I have been elected to be head of the Social Statistics Section of the American Statistical Association. I have held several positions concerning grant review committees for national government, and I have worked with the United Nations on numerous assignments abroad. I have also served as a peer reviewer for such journals as the New York State Journal of Medicine, Medical Care, and The American Journal of Public Health, etc. I have served on committees with respect to areas that involve epidemiology, including committees for the National Center for Health and Services Research and Health Care Technology; for the Department of Health and Human Services; and I served as a consultant to the National Center for Health Statistics, the National Institute on Aging, and others. One of the recent courses that I taught was titled "Epidemiology, Biostatistics,

[4]

and Public Health."

I have more than 30 articles in refereed journals in the fields of biostatistics, epidemiology, and biometry.

2. I have reviewed the epidemiology studies that pertain to Bendectin.

3. I have been appointed by the Federal Bankruptcy Court in the Dalkon Shield cases to do epidemiological analysis.

4. In examining epidemiology studies, one must keep in mind that there are numerous difficulties associated with trying to do such studies with expected birth defects. These difficulties include precisely what drugs were given in [addition] to the drug being tested and when were they given; what are the characteristics of the persons involved; what is the reproductive history of the individuals in the study; what is the reliability of the study, etc. When one is looking at a defect that is rare, these difficulties increase in magnitude with respect to the drug being examined.

5. In reviewing the various epidemiological studies, one must utilize one's training, education and experience as an epidemiologist, and analyze the data in order to be able to render an intelligent opinion. One must look at this study closely, analyze it,

and determine the quality of its methodology.

When one looks at the epidemiology studies pertaining to Bendectin, one finds that there are in fact studies that do

[5]

show a statistically significant association between Bendectin and birth defects, even at the 95% confidence level. Moreover, because of the weakness of the epidemiological information one needs to look at all of the available epidemiological data in order to determine whether or not a drug is generally a teratogen. In that regards, all the studies are helpful and informative in some regard.

I have reviewed numerous epidemiological articles including those by Aselton, Eskenazi, Cordero, Jick, etc.

6. In my opinion, it would not be good, and generally accepted, and reasonably accepted, epidemiological practice to ignore data that might be in an article dealing with one injury such a pyloric stenosis in maternal Bendectin exposure or an article that dealt with heart defects or cleft palate if one was attempting to determine whether o[r] not a drug was capable of causing a defect in the limbs. It would be wrong to ignore those studies. Standard practice would be to examine such studies.

One must always keep in mind that when one looks at the epidemiology studies one primarily deals with statistical data of the population and not for individuals. A statistical association that may be made at the 95% confidence level does not by itself mean that a member of that group developed a defect merely because he was in the positive group. Likewise, the statistical data therefore can only give a guideline with respect to an analysis on whether or not a drug is a

[6]

teratogen. In other words, association means that one thing is related to the other, but it does not mean that the one thing causes the other. Likewise, a failure to show a statistical association does not mean that there is not a causal connection.

When one looks at the epidemiological dat[a] on Bendectin and using my education, training and experience, it is my opinion that within a reasonable degree of epidemiological certainty that there is evidence that shows that there is a statistical association between Bendectin and various birth defects. In making this analysis, I used the methodology and techniques that are generally and reasonably relied upon by persons who are trained with respect to biostatistics, biometry, and epidemiology.

7. When one looks at the studies known as Cordero, Eskenazi, and McCredie, one finds that in each case the data in that study showed a point estimate of the relative-risk that was greater than

one which indicates that the risk of developing a child with a limb defect was greater when Bendectin was taken than when it was not taken. None of the studies could be interpreted as being negative studies. Further, when one looks at each of these three limb reduction studies, considering the relative risks that are developed, considering that various problems and limitations with the studies exist, using my education, experience and training with respect to public health, epidemiology, biostatistics,

[7]

biometry, and utilizing the methodology that is generally and reasonably relied upon, within a reasonabl[e] degree of epidemiological certainty, there is a statistical association between Bendectin and limb defects. Moreover, when one looks at the limb studies just referred to along with the other studies on cleft palate, pyloric stenosis, and heart malformations, once again using my education, experience, and training, and the methodology that is generally and reasonably relied upon in the field, it is my opinion within a reasonable degree of epidemiological certainty that Bendectin is associated with limb defects and other birth defects, as well.

8. A review of the Jick data that was collected and supplied to me shows that such is in fact another collection of a body of data that statistically significantly associates Bendectin and limb defects.

9. Further, based on my education, training and experience and reviewing the epidemiological articles that pertain to Bendectin, it is my opinion that within a reasonable degree of epidemiological certainly utilizing the techniques that are generally and reasonably relied upon by biometrists, and biostatisticians that Bendectin is within a reasonable degree of epidemiological certainty associated with congenital disorders, including limb defects.

10. To the best of my knowledge, I have reviewed all of the published epidemiological data on Bendectin.

[8]

11. In sum, when one uses one's education, training and experience and generally and reasonably relied upon methodologies for review, I am of the opinion that within a reasonable degree of epidemiological certainty that there is in fact a statistical association between Bendectin and birth defects including limb defects.

/s/
Jay H. Glasser

STATE OF

COUNTY OF

Subscribed and sworn to before me this 27th day of September, 1989.

/s/
Notary Public

CURRICULUM VITAE

Jay Howard Glasser, Ph.D., Associate Professor
Biometry and Computer Services
School of Public Health
Post Office Box 20186
The University of Texas
Houston, Texas 77025
Office: 713-792-4372 Phone: 713-729-9749

Educational Qualifications:

1957 B.S.
University of Connecticut
Zoology - Mathematics
1960 M.Sci.
Columbia University
Biostatistics
1967 Ph.D.
North Carolina State University
Experimental Statistics

Professional Experience:

Convener - Biometry Discipline, School of Public Health, The University of Texas, Houston, Texas, September 1984 - Present.
Associate Professor of Biometry and Computer Sciences, School of Public Health, The University of Texas, Houston, Texas, September 1969 - Present.
Visiting Senior Lecturer, Department of Community Medicine, St. Thomas' Hospital Medical School, London, England, 1974-1975.
Senior Investigator, Kaiser (Portland) Health Service Research Center, Kaiser Foundation Hospitals, 1970 - 1982.
Visiting Faculty in Graduate Summer Session of Statistics in the Health Science, School of Public Health, University of California at Berkeley, 1971 - 1972.
Consultant in Residence (Washington, D.C.), National Center for Health Services Research and Development, Summer 1970; National Center for Health Statistics, Summer 1967, 1968 and 1976.

Assistant Professor, Department of Biostatistics and Carolina Population Center, University of North Carolina, Chapel Hill, North Carolina, 1967-1969.
Instructor, Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, 1964-196[ ].
Visiting Lecturer, Duke University, School of Nursing, 1963-1969.
Assistant Statistician, New York City Health Department, 1957-1958.

Recent Consultant Positions:

American Association for the Advancement of Science
American Association for Vital and Health Statistics
Baylor College of Medicine (Department of Pediatrics) and Texas Childrens Hospital
McDonnell Douglas Corporation
National Academy of Science (Institute of Medicine)
National Center for Health Service Research and Health Care Technology Assessment (DHHS)
National Center for Health Statistics (DHHS)
National Institute on Aging
National Institute of Heart, Lung, and Blood Institute
National Institute for Occupational Safety and Health
United Nations
United States Courts Eastern District of Virginia, (Robins-Dalkon Shield Litigation)
Veterans Administration
World Health Organization (Geneva, Switzerland)

Honors and/or Special Awards:

Research Scientist - Career Development Award (Health Services Research) U.S. Department of Health, Education and Welfare, 1971-1976.
Fellow, Royal Statistical Society, United Kingdom, 1974.
Fellow, American Public Health Association, 1969.
Sigma Xi, 1968.
National Institute of Health Fellowship, 1958-1964.
Public Health Traineeship, 1959-1960.
Research Fellowship, Marine Biological Laboratory, 1956.

Professional Societies:

American Public Health Association
Committee on American Statistical Association (1987-89)
Biometrics Society
Inter-American Statistical Institute

Professional Society and Academic Offices:

Chair, Statistics Section, American Public Health Association, 1986-87.
Member: Committee on International Relations in Statistics, American Statistical Association, 1987- 1989
Member: Committee on Quality Assurance in Patient Care, The Medical School, The University of Texas Health Science Center, 1987-Present
Chair-Elect and Program (Chair, Statistics Section, American Public Health Association, 1985-1986
Convener, Biometry Faculty, School of Public Health, The University of Texas, 1984-Present
Associate, Program in Health Care Technology and Ethics, University of Texas Health Science Center, 1984-Present
Executive Board, American Statistical Association, Social Statistics Section, 1981-1982 (ex-officio).
Chair, Membership Committee, American Public Health Association, Statistics Section, 1981-1982.
Chairman, American Statistics Association Social Statistics Section, 1980-1981.
Action Board, American Public Health Association, 1975-1977 term.
Convenor, Health Services Organization Faculty, School of Public Health, the University of Texas, 1973-1974, 1975-1977.
Statistics Section Council, American Public Health Association, 1970-1973.
Chairman, Academic Affairs Committee, School of Public Health, The University of Texas, 1969-1970.
Faculty Council, The University of North Carolina 1968-1971 term (an elective office).
Program Committee and Chairman, Statistics Section, American Public Health Association, 1968-1969.

National and State Advisory and Review Committees:

Expert: United States Court, Eastern Division of Virginia (Epidemiological and Statistical evidence for litigation of the Robins-Dalkon Shield IUD claims before the Court), 1986-present.
Chairman, Family Planning, adhoc Special Review Committee, Office of Population, Department of Health and Human Services (DHHS), 1983-1987.
Member, adhoc Nursing Research Review Group, National Institutes of Health, 1985 and 1986.
Member, Health Services Developmental Grant Review Subcommittee, National Center for Health Services Research (DHHS), October 1982 - July 1986 term.
Member, ad hoc Program Grant Review Committees, National Institute on Aging (DHHS), 1982, 1984, 1985.
Chairman, Special Review Group Health Hazard Evaluation and Occupational Health Surveillance, National Center for Occupational Health and Safety (DHHS), 1980-1981 and 1982.
Member: Nursing Study, Trends and Forecasting Panel, Institute of Medicine, National Academy of Sciences, 1981.
Member: Health Planning Center Council, Region VI Center for Health Planning, 1976-1979.
Member: The University of Texas System Group on Health Policy Development, 1978-present.
Health Services Research Review Committee, National Center for Health Services Research (DHHS), July 1977 - June 1981 term.
Task Force on Training, National Center for Health Statistics, 1976-1978.
HMO Advisory Committee, Health Resource Department, State of Texas, 1975-1976.
Research in Nursing and Patient Care Review Committee, Division of Nursing (DHEW), July 1970 - June, 1974 term.
Member of Federal-State-Local Data Systems Review Committee, National Center for Health Services Research and Development, 1972-1973.

Miscellaneous:

Committee on Federal Statistics for Public Health, American Public Health Association, 1981 - present.
Health Profiles for Hazardous Waste Disposal Sites and Incineration Operations. State of Missouri, 1981 - present.

Joint Ad Hoc Committee on the Assessment of National Data Resources for Biomedical Research, American Public Health Association, 1970 - 1979.
Epidemiologic Analysis Committee, National Center for Health Services Research (DHEW), 1969 - 1974.

Training, Workshop and Materials Development:

Local Coordinator and Organizer: Workshop on the National Health Centers Health Interview Survey (1987), Sponsored by the National Center for Health Statistics, DHHS.
Presenter and Resource Person: Uses of Statistical and Epidemiological Data in Legal Testimony Association of Consulting Toxicologists, 1987.
Local Coordinator and Organizer: Hispanic Health and Nutrition Examination Survey Data Tape Workshop (HHANES), 1986. Sponsored by the National Center for Health Statistics, DHHS.
Seminar Director and presenter "Microcomputers for Managers" developed and presented for The Social Security Administration (U.S.) 1984. A seminar series for managers on the use, and implementation of microcomputers in local offices. The course included hands-on instruction including modules on data processing, workflow, scheduling and word processing. No prior experience in computers was assumed.
Course Director: "Reimbursement and Rate Setting Concepts," Applied Statistics Training Institute, National Center for Health Statistics (DHHS). July 1981 and June 1982. A course on cost containment, rate setting and financial management for health care institutions and delivery agencies.
Seminar and workshop on Human Resource Development Applied to Nurse Recruitment and Retention Studies (1982).
Seminar on Cost Benefit-Cost Effective Methodology Applied to Occupational Health (1982).
A series of modular courses on Program Evaluation, Cost Benefit-Cost Effectiveness Analysis, selected topics in Demographic Analysis and Indices of Health. Development jointly with colleagues and pretested for the Applied Statistics Training Institute (National Center for Health Statistics, DHHS) (1978-1980).
Course Director: "Statistical Methods in Health Service Delivery and Administration," Applied Statistics Training Institute, National Center for Health Statistics (DHHS). Annual Presentations, 1971-1981. A course on quantitative techniques and [information] systems use and development directed to

administrators, planners and evaluators.
Developed and presented a series of education television tapes on Biostatistics (part of a course, "Foundations in Public Health"), November 1968 - January 1969.
Source Book in Health Policy Analysis and Quantitive Techniques. The use and role of epidemiological, statistical and demographic techniques in the development and evaluation of health policy (in process).

International:

Organizer and Presider, Seminar on Methods of Medical Technology Assessment, Tekmed Congress 1987, Lyon, France.
Course Director and faculty member: Epidemiology, Statistics, and Experimental Design in Public Health. Presented at the University of Panama, Republic of Panama, 1987. Sponsored by the American Association for the Advancement of Science and Consortium for Universities in Central America.
Consultant in further development and implementation of a complete registration training program and subsequent adaptation for Jamaica. This on-going project is jointly sponsored by the Registrar General's Office of Jamaica, the National Center for Health Statistics and AID-Jamaica (1980-1986).
National Conference on Vital Statistics and Registration Improvement and Training in Program Evaluation Research in Family Planning (National Family Planning Board of Jamaica and AID-Jamaica) (project pending).
Consultant: American Public Health Association. Evaluation of the Contraceptive Prevalence Study Program. Agency for International Development (1983).

Other International Consulting and Experience:

Consultant and participant: African Regional Conference on Contraceptive Prevalence Studies (Westinghouse Systems), Harare, Zimbabwe (March-April 1983).
Member and Secretary: United Nations - Expert Panel on Revision of the The Handbook on Registration and Vital Statistics, 1983-1985.
Consultant to the Ministry of Health, the United Arab Republic of Egypt for the Health Profile of Egypt. Analysis of the Health Interview and Health Examination Survey results (sponsored

jointly by the Ministry of Health and the National Center for Health Statistics (March-April 1982 and March-April 1983).

Developed a Modular Course in Vital Statistics Improvement and Civil Registration Training (with E.S. Lee). A 20-module training course in Vital Statistics and Management Techniques for Vital Statistics Improvement in Developing Nations. Developed for the VISTIM Program, National Center for Health Statistics (DHHS) (1977-1979).

Visits to Denmark, England, Israel, Norway, Sweden and U.S.S.R. to observe and meet colleagues in health services delivery, planning, administration research, and training (1974, 1975, 1977, and 1980).

Visits and consultation with WHO European Regional Office and WHO Geneva (1974-1975, 1982-1986).

Visits to Pakistan and India to study the feasibility of establishing population measurement laboratories (sponsored by the Population Center, the University of North Carolina and US-AID) (1968).

Current Duties:

Teaching: Various courses in basic and advanced topics in biostatistics, epidemiology and population research techniques and applied research in community health; planning, monitoring and evaluation. Developing modular courses and source book material in health services delivery, policy analysis, trend and forecasting analysis and technology assessment.

Consulting: General consulting in health sciences clinical trials and health services research with particular emphasis on program and study designs, survey research and information systems, analysis of data and quantitative evaluation of delivery systems. Consulting includes the use of microcomputers, workshops and seminar development to upgrade practicing health professionals' skills, epidemiological and statistical analysis of health hazards with emphasis on monitoring and legal applications.

Research: Measurement in health service research, policy analysis, technology assessment, delivery systems and community health programs stochastic models in the biological sciences and demography. Recent areas of research include utilization analysis, trend and impact analysis, epidemiological basis for population health hazards monitoring, mental health, and eldercare.

Publications:

J.H. Glasser, "Strategy for Improving Coverage, and Quality of Registration and Statistics". A chapter in Handbook on Methods for Vital Statistics and Registration. The United Nations. In press.

J.H. Glasser, "Health Statistics Surveillance Systems for Hazardous Substance Disposal" in Proceedings of the 1985 Public Health Conference on Records and Statistics, The National Center for Health Statistics, DHHS Publication No. (PHS) 86-1214 (1986)

J.H. Glasser, "Implications of the Declining Mortality for The Organization of Health Care: The Case of Jamaica" in New Developments in the Analysis of Mortality and Causes of Death, edited by H. Hansluwka, et.al. World Health Organization, Geneva, Switzerland 1986.

J. Mangaroo, J.H. Glasser, L. Roht and A. Kapadia, "Prevalence of Bone Dimineralization in The United States." Bone (Formerly Metabolic Bone
Disease and Related Research). Vol 6, March 1985, p. 135-139.

B.L. Levin, J.H. Glasser, "A National Survey of Prepaid Mental Health Services."
Journal of Hospital and Community Psychiatry. Vol. 35 No. 4, April 1984

B.L. Levin, J.H. Glasser and R.E. Roberts, "Changing Patterns in Mental Health Services Coverage Within Health Maintenance Organizations." American Journal of Public Health. Vol. 74, No. 5, May 1984.

J.H. Glasser and J. Wolfson, "Rocky Road, the Flavor of Health Services Research." Medical Care. Vol. 21, No. 9, September 1983, pp. 393-942.

J.H. Glasser, "Teaching of Statistics in Health Administration." Proceedings of the Social Statistics Section, American Statistical Association. August 1982.

J. Mangaroo, J.H. Glasser and A. Littel et al., "Networking Micro-Processors for Effective Computer Utilization in Nursing." Proceedings of the Sixth Annual Symposium on Computer Application in Medical Care IEEE Computer Society. Library of Congress No. 79-641114, p. 575, November 1982.

D. Lairson, R. Forthofer, and J.H. Glasser, "Medical Care Utilization in a Regional Prepaid Medical System. " The Annals of Regional Science. Vol . 16, No. 2, July 1982, pp. 62-72.

J . H . Glasser, "Quality and Utility of Death Certificate Data. " American Journal of Public Health. Vol. 71, No. 3, March 1981.

M. Rush and J.H. Glasser, "Lightning Risk." Reviews on Environmental Health, Vol. III, No. 3, 1981, pp. 301-313.

R. Forthofer, D. Lairson and J.H. Glasser, "Catastrophic Insurances and HMOs." Social Science and Medicine. Vol 16, No. 3, pp. 1775-1779, March 1981.

B.L. Levin and J.H. Glasser, "Mental Health Coverage Within Prepaid Health Plans." Administration in Mental Health, Vol . 7, No. 4, Summer 1980, pp. 271 -281.

D. Lairson, R. Forthofer and J.H. Glasser, "Catastrophic Illness in an HMO." Inquiry, Vol. XVI, No. 2, Summer 1979, pp. 119-130.

R. Forthofer and J. H. Glasser, "Utilization of Services of an HMO by New Enrollees." American Journal of Public Health, Vol. 69, No. 11, November 1979, pp. 1127-1131.

B.L. Levin and J H. Glasser "A Survey of Mental Health Service Coverage Within Health Maintenance Organizations." American Journal of Public Health, Vol. 69, No. 11, November 1979, pp. 1120-1125.

R. Forthofer, J.H. Glasser and N. Light, "Life Table Analysis of Membership - Retention in an HMO." Journal of Community Health, Vol 5, No. 1, Fall 1979, pp. 46-53.

J.H. Glasser, R. Roberts, O. McCrory and C. Askew, "Dental Care for Handicapped Children Re-examined: I. Dental Training and Treatment of the Handicapped." Journal of Public Health Dentistry, Vol. 38, No. 1, Winter 1978, pp. 22-34.

D. Lairson, R. Forthofer and J. H. Glasser, "Catastrophic Expenditures: Family Experience in an HMO. " Third Data Use Conference, Part [I]. Health Planning Information Series, DHEW, Publication HRP-C201-1401 (1978).

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J.H. Glasser, R. Roberts, and O. McCrory, "Specialized Training for Dentists Treating Children with Handicaps." Department of Health, Education and Welfare, Bureau of Community Health Services, Publication No. (HSA) 78-5218, 1978, pp. 119-130.

J.H. Glasser, "Research Needs for Data Applications in Health Planning." Proceedings of the Public Health Conference on Records and Statistics, 16th National Meeting, DHEW National Center for Health Statistics, DHEW Publication No. (HRA) 77-1214 (1977).

Florence Lee and J.H. Glasser, "Role of Lay Midwifery in Maternity Care in a Large Metropolitan Area." Public Health Reports, Vol. 89, No. 6, November-December 1974, pp. 537-544.

D. Basco, S. Eyres, D. Roberts and J.H. Glasser, "Epidemiologic Analysis of School Populations as a Basis for Chance in School Nursing Practice: Report of the Second Phase of a Longitudinal Study." American Journal of Public Health, Vol. 62, No. 4, April 1972, pp. 491-497.

J.H. Glasser, "Health-Information Systems: A Crisis or Just More of the Usual?" American Journal of Public Health, Vol. 61, No. 8, August 1971, pp. 1524-1530.

J.H. Glasser, "A Stochastic Model for Industrial Illness Absenteeism." American Journal of Public Health, Vol. 60, No. 10, October 1970, pp. 1936-1944.

A. Kaluzny, J. Gentry, and J.H. Glasser, "Diffusion of Innovative Health Care Services in the United States." Medical Care, November-December 1970, Vol. 8, No. 6, pp. 474-487.

J. Gentry, A. Kaluzny and J. Sprague and J.H. Glasser, "Perceptual Difference of Administrators Regarding the Importance of Health Service Programs: Implications for Education for Health Service Administration." American Journal of Public Health, Vol. 60, No. 6, 1970, pp. 1006-1017.

J.H. Glasser, "Conceptual Issues in the Selection of Statistical Techniques for the Analysis of Medical Care Utilization Behavior." HEW (National Center for Health Services Research), October 1969.

D. Basco, S. Eyeres, D. Roberts and J.H. Glasser, "Epidemiologic Analysis in School Populations as a Basis for Change in School Nursing Practice." American Journal of Public Health Vol. 59, No. 12, December 1969, pp. 2157-2167.

J.H. Glasser and P.A. Lachenbruch, "Observation on the Relationship Between Frequency and Timing of Intercourse and the Probability of Conception." Population Studies, Vol 22, No. 3, 1968.

A. Kluzny, J. Gentry and J.H. Glasser, "Innovation in Health Care Research and Plan of Project Studies. " Health

A. Kluzny, J. Gentry Organizations: Review of Services Research, Vol 3, No. 4, Winter 1968, pp. 316-326.

"A Stochastic Model for Industrial Absenteeism." Unpublished doctoral dissertation, North Carolina State University, April 1967.

Miscellaneous Publications:

B.L. Levin and J.H. Glasser, "Preliminary Results from the 1982 National Survey of Psychiatric Services and Coverage Benefits With Health Maintenance Organizations." In D.Y. Patterson (ed): Report of the Task Force on Health Maintenance Organizations . American Psychiatric Association . In press.

J.H. Glasser, E.S. Lee and R. Forthofer, "Discussion of Methodologic Papers of the National Center of Health Statistics." Proceedings of the Social Statistics Section. American Statistical Association, August 1978.

Recent Commissioned or Invited Papers and Seminars

J.H. Glasser, The Aim and Methods of Assessment of Medical Technologies, Tekmed Congress, 1987, Lyon, France.

Institute of Social and Preventive Medicine, University of Lausanne (Switzerland) Seminars on: Meta Analysis in Health Care Research, and The Role of Statistics and Epidemiology in Environmental and Occupational Health (1986)

Methods of Analysis for Populations Exposed to Environmental Health Hazards, California State University, San Diego (1986)

John Lawson, and Jay H. Glasser, "Analysis and Profile Methods for Child Survivorship Research". Invited paper: American Public Health Meetings, 1986.

Health Profiles for Hazard Waste Disposal and Hazard Waste Incineration Operations. A series of profiles for monitoring the health of populations potentially exposed to environment contaminants around hazardous waste site impoundments or incinerator operations. State of Missouri (1981-1986).

Overview of Analytic Issues in Using The National Center for Health Statistics Public Use Tapes, the National Center for Health Statistics Data Tape Users Conference. Summer, 1986

Miscellaneous Publications: (Continued)

Use of Secondary Data in Health Statistics Analysis, National Center for Health Statistics Data Tape Users Conference. Summer 1984.

Health Profiles for Hazardous Waste Site Monitoring Data Use Conference on Small Area Statistics, National Center for Health Statistics. Summer 1984.

Westinghouse, Public Applied Systems: "Population and Family Planning: Data, Analyzing and Management Decision Applications" (March 1983).

Statistics Section, American Public Health Association, Lowell Reed Invited Lecture. Annual Meetings (November 1983).

UNITED STATES DISTRICT COURT
Western District of Washington at Tacoma

No. C83-74TB

LYNN ANNETTE HILL, et al.,
Plaintiffs,

v.

MERRELL DOW PHARMACEUTTICALS, INC., et al.,
Defendants.

Deposition of JAY H. GLASSER, a witness of lawful age, taken on behalf of counsel for the Plaintiffs in the above-entitled matter, pursuant to notice, before Shirley D. Jones, Notary Public, at the law offices of Paulson, Nace & Norwind, 1814 N Street, N.W., Washington, D.C., commencing at 12:27 p.m., Thursday, March 3, 1988.

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Q. Doctor, when one looks at these three limb reduction studies, considering the relative risks that are developed there, and considering the various problems or limitations within the studies themselves that you talked about, using your experience, your education, and your training with respect to public health, epidemiology, biostatistics, and biometry, putting all that together in your area that you have worked in all these years, looking at those three studies that, in some respect, involve the limbs, would you be able to come up with an opinion within a reasonable degree of epidemiological certainty as to whether or not there is a statistical association between Bendectin and limb defects?

A. Well, I had concluded that, in a preponderance of all the data in the studies, that there is --

MR. WOODSIDE: I object to the question. Does he have an opinion?

BY MR. NACE:

Q. First of all, do you have an opinion?

A. Yes.

Q. What is that opinion?

A. My opinion is that in the preponderance of these studies, I believe the weight of them is that there is an association.

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there has been no foundation from either an epidemiologic or other scientific standpoint for him to give such an opinion, and because it includes birth defects other than those which are the subject matter of this litigation.

BY MR. NACE:

Q. You may answer.

A. I believe that there is an association between -- from the sum and substance of the literature that I reviewed and from my point of expertise, that it has an association of Bendectin with congenital disorders.

MR. WOODSIDE: I move to strike.

BY MR. NACE:

Q. Doctor, have you previously been qualified in federal courts in this country to give testimony with respect to Bendectin?

MR. WOODSIDE: Objection. It is an irrelevant consideration in questioning.

THE WITNESS: Yes.

BY MR. NACE:

Q. Do you recall where those courts were?

A. In Kansas City, Missouri and in Tyler, Texas.

Q. Finally, I have one more series. I am going to show you -- You may have seen this exhibit, 441 for identification.

* * *

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Bendectin, do you?

A. No, I do not.

Q. You do not have any publications that deal with the components of Bendectin, such as doxylamine; correct?

A. Correct.

Q. You have never published any articles in the peer reviewed literature dealing with antihistamines, have you?

A. No.

Q. Nor with anti-nauseants or anti-emetics; correct?

A. Correct.

Q. In addition, you have never published any articles in the peer reviewed literature dealing with birth defects; correct?

A. Well, no.

Q. When you say no, you mean, yes, I'm correct, you have not published any?

A. No. I have published some work on death certificates, which contain information. But that is not a major area of my expertise.

Q. You have not published any articles in the medical literature dealing with teratology, embryology, or pharmacology; have you?

A. Correct.

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Q. You don't consider yourself to be an expert in those areas, do you, sir?

A. No.

Q. You have not made any presentations of a scientific nature before any professional or scientific groups dealing with Bendectin and/or its components, have you?

A. No.

Q. You have not performed any epidemiologic studies on Bendectin or its components, have you?

A. No.

Q. You have done no original studies of an epidemiologic nature with respect to birth defects, correct?

A. Correct.

Q. You have done no case control studies on illnesses or birth defects, correct?

A. On illnesses and birth defects?

Q. On illnesses or birth defects, case control.

A. I have participated in case control studies.

Q. On illnesses or birth defects?

A. On illnesses.

Q. What kind of illnesses have you performed case control studies on?

A. I've looked at a series of cases in the National Eye

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A. Yes.

Q. And there is the epidemiology area?

A. Yes.

Q. You are the convener in the biometry area, correct?

A. Yes.

Q. You are not in the epidemiology area, correct?

MR. NACE: I have to object. What do you mean by "in"? I don't understand the word.

BY MR. WOODSIDE:

Q. Do you have an appointment in the epidemiology area?

A. No. Currently, we can have only one appointment in one of the disciplines.

Q. So that your appointment is in the biometry discipline, as opposed to the epidemiology discipline; correct?

A. Correct.

MR. WOODSIDE: Be off the record for just a second here. I have got to find something here.

(The deposition was briefly suspended in place.)

BY MR. WOODSIDE:

Q. You do not consider yourself to be an expert in epidemiology, do you, sir?

A. No. As I have explained in the past, I believe that my expertise is in biometry, with a secondary application in

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epidemiology.

Q. Just so I'm clear, the answer to my question was no; correct?

MR. NACE: I object. The answer is what you got.

BY MR. WOODSIDE:

Q. Was the answer to my question no?

A. I tried to give you a complete answer to your question.

Q. Sir, do you recall that you gave testimony in Kansas City, Missouri on December 7, 1987 in a case styled Barbara Susan Rudell and others v. Merrell Dow Pharaceuticals, Inc?

A. Yes, I do.

Q. Sir, do you recall that on that occasion, you were asked the following question and gave the following answers: "Okay. Now, you do not consider yourself to be an expert in epidemiology, do you, sir?" Answer: "No." Sir, do you recall that question and that answer?

A. Yes, I do.

Q. Sir, you were under oath at that time; were you not?

A. Yes.

Q. And you told the truth; did you not, sir?

A. I did not finish my sentence.

Q. Did you tell the truth?

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A. Yes.

Q. Thank you. Sir, do you recall a case styled David A. Barton and Tamara T. Barton v. Richardson Merrell, Inc.? Sir, do you remember that your deposition was taken on September 2nd and 3rd, 1987 in a case called David A. Barton and Tamara T. Barton v. Richardson Merrell, Inc.?

A. Yes.

Q. Do you recall, sir, on that occasion that you were asked the following question and gave the following answer: "Do

you consider yourself or do you put yourself out as an expert in epidemiology?" Answer: "No, not as -- no, no, I do not." Did you give that testimony on that occasion, sir?

A. As I recall, yes.

Q. Did you tell the truth at that time, sir?

A. Yes.

Q. Are you familiar with an organization known as ACT or the Association of Consulting Toxicologists?

A. Yes. I am familiar with something called the Association of Consulting Toxicologists.

Q. Sir, that is an organization which makes arrangements for individuals to testify on occasion; correct?

A. I understand that's part of what they do.

Q. In some instances, they basically obtain witnesses to

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necessary, Mr. Nace, I will be glad to demonstrate that.

MR. NACE: Absolutely.

BY MR. WOODSIDE:

Q. I would like to ask you a number of questions about your opinion testimony that you have given in this particular case. First of all, it is true, is it not, that there is no epidemiology study looking at limb defects in humans where the authors conclude there is a statistically significant association between the ingestion of Bendectin and limb reduction defects in the offspring; correct?

A. Correct.

Q. I believe you indicated that you had read or reviewed a number of epidemiology studies relating to Bendectin. Correct?

A. Correct.

Q. And I believe you indicated that some of those studies were better than others. Is that a fair statement?

A. Correct.

Q. But you did, in fact, consider all of the studies for whatever value they may have been.

A. Yes.

Q. There is, in fact, an epidemiological or biostatistical technique known as pooling or metaanalysis;

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the same as a cause and effect relationship. Correct?

A. Correct.

Q. Epidemiologic studies are designed to determine whether there is or is not an association; correct?

A. Correct.

Q. Even if one gets an association in an epidemiologic study, that does not mean that there is a cause and effect relationship; correct?

A. Correct.

MR. NACE: Wait a minute. I object. Do you mean automatically? I don't understand your question. Always, automatically, or generally?

MR. WOODSIDE: I'll expand upon the question.

BY MR. WOODSIDE:

Q. The mere fact that in an epidemiologic study there is a statistically significant association does not mean, without more, that there is a cause and effect relationship; correct?

A. Well, again, I think one needs to look at exactly what it is one is trying to accomplish. In a clinical trial, which is a prospective cohort study, we may have set up hypotheses to be tested in advance that would give a cause and effect inference in the sense of the polio myelitis example. That was set up as a prospective cohort study, randomized populations

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among the treatment and control group, and then tested for the significant protective effect of the Salk polio trial.

Now, in that sense, I would say that was looking towards a cause and effect relationship. With a case control study, we are looking more towards the association aspect.

Q. In the Bendectin studies which you reviewed, there were case control and cohort studies; correct?

A. But no clinical trials.

Q. That's where we going, okay?

A. Correct.

Q. I'll get back to the clinical trials question in a minute.

A. I didn't mean to anticipate your line of questioning.

Q. That's quite all right. Let me ask the question again, and you'll see where I'm going. In the Bendectin studies that you reviewed, there were both case control and cohort studies; correct?

A. Correct.

Q. In those studies that you reviewed, there were no

controlled clinical trials; correct?

A. Correct.

Q. In the studies that you reviewed, they were trying to determine whether there was an association or not between

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Bendectin exposure and the development of birth defects; correct?

A. Correct.

Q. In those studies, they were not attempting to determine whether, based upon the studies alone, there was a cause and effect relationship; correct?

A. Well, again, there is a difference between the statistics and the design and the conclusions or inference that various authors drew. So, again, there is not necessarily "statistics", and that's it. It was the interpretation that various people placed on them that was also in the literature.

Q. In those studies that you have referred to on Bendectin, that is, both the case control and the cohort studies, none of the authors concluded in their studies that Bendectin caused birth defects; did they?

A. Correct.

Q. Let me ask you a question about controlled clinical trials for a minute. Did I use the right term?

A. That's fine.

Q. That the term you used a minute ago?

A. (Nodding head up and down.)

Q. Have you ever seen or reviewed any controlled clinical trials on Bendectin?

* * *

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limb defects in which the relative risk is increased and the confidence intervals do not include 1?

A. When you say "published articles," do you mean the article in the Journal of the American Medical Association?

Q. Let me go back and make sure my question is correct.

MR. NACE: I'm going to object. I think a simple answer -- You can answer his question. He asked about J-A-M-A, JAMA.

MR. WOODSIDE: You'll see where I'm going.

BY MR. WOODSIDE:

Q. You indicated in your direct testimony that you

reviewed a number of publications dealing with Bendectin and limb reduction defects which appeared in peer reviewed scientific or medical journals; correct?

A. Correct; and also associated reports or background documents, though.

Q. I'll get to that in a minute.

A. Okay.

Q. For the purpose of my question that I'm now asking you, I want to limit the scope of my question to those articles which have been published in peer reviewed medical or scientific journals, okay?

A. Okay.

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Q. I will get to the other things in a minute, I assure you. Directing your attention again to the concept of evidence of association as it appears on that chart, I have the following questions. It is true, is it not, that there are no epidemiologic studies published in the peer reviewed medical or scientific literature looking at limb reduction defects in which there was evidence of an association between the Bendectin exposure and limb reduction defects?

A. Oh, no. I would say there are many articles that indicate evidence of it, but in the sense that I would use that word.

Q. Today, in this litigation, you have referred to "evidence of association" in putting materials on the board in relating and referring to the Mitchell article; correct?

A. Correct.

Q. For the purposes of this question, I am utilizing the terms "evidence of an association" the way Dr. Mitchell and others used it and the way you used it when you referred to their article and explained certain epidemiologic techniques, okay?

A. Okay.

Q. In the epidemiology studies looking at limb reduction defects and Bendectin that have been published in peer

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reviewed, refereed, scientific or medical journals, there are none in which there is evidence of an association as utilized in the Jicks -- excuse me -- as utilized in the Mitchell article about which you have testified on your direct examination?

MR. NACE: I'm going to object. You can tell us

what articles you are referring to.

MR. WOODSIDE: Any.

MR. NACE: Well, you imply that there are many that were done, Mr. Woodside. What are you referring to? How many were done?

MR. WOODSIDE: He came in and gave a bunch of testimony. I want to know if in the articles that he reviewed he found any dealing with epidemiology studies looking at limb reduction defects and Bendectin that have been published in the literature that he has reviewed.

MR. NACE: I object to that as being an unfair question. You are asking a negative question that presupposes that there must be a negative answer. Improper.

MR. WOODSIDE: The question is perfectly acceptable.

MR. NACE: No, I think it is not acceptable. I think it is phrased in such a way -- It is one of those questions that is designed solely to get an answer that will satisfy you

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but not necessarily be accurate and lead to the truth of the matter.

BY MR. WOODSIDE:

Q. Doctor, can you answer my question?

A. Well, I'm trying to distinguish two things that you are asking about in this sense versus the metaanalysis sense that you were asking about before. So, you are confining yourself to the --

Q. To the individual articles.

A. No. There are no individual articles that flatly come out and conclude that there is an evidence of association in the sense that it is written -- given up there, as its total and final conclusion.

Q. As it relates to limb reduction defects, there are no epidemiologic studies published in the peer reviewed scientific literature dealing with Bendectin in which there is an elevated relative risk and the 95 percent confidence intervals do not include one; correct?

MR. NACE: I object to the relevancy of that question.

MR. WOODSIDE: Fine.

BY MR. WOODSIDE:

Q. Can you answer my question?

A. No.

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Q. Meaning, no, I am correct, there are no such studies?

A. You are correct.

Q. In those epidemiologic studies where there is an increased relative risk but the confidence intervals include 1, you have indicated that the result is inconclusive; correct?

A. Correct, for a given -- right; any one given confidence interval.

Q. Right; in any one given study?

A. I mean, that's part of the problem I'm having with answering your question because each of these articles, as we have gone over, have many different confidence intervals looking at different conditions. And that's where I have -- There is no one article that has one confidence interval. It often has many different confidence intervals looking at many different aspects. So, the difficulty that I'm having -- and I'm going to try to answer as precisely and clearly as possible -- is that the thrust of what you seem to be saying is as though there was one confidence interval within one article, and that is it.

Q. I don't believe I asked that question. I was referring to the confidence intervals in studies that same way you were when you were referring to Dr. Mitchell's article and writing things on the board, or whatever you call this thing.

* * *

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A. Correct.

Q. Sir, this study deals with oral clefts; correct?

A. Correct.

Q. You do not know when you would have to administer a substance during gestation for it to cause oral cleft, do you?

A. No.

Q. So that you don't know if the administration of a drug at the end of the eighth or ninth weeks would be too late to cause a birth defect of this type or not, do you?

A. Correct.

Q. Would you turn for just one minute to Plaintiffs' Exhibit 519, which is the study by Rothman and others entitled "Exogenous Hormones and Other Drug Exposures of Children with Congenital Heart Disease." In particular, if you would refer to Table 1, please.

A. (Examining) Yes, sir.

Q. I believe you had referred to that table during your direct examination. Correct?

A. Correct.

Q. I believe, in particular, you looked at the line dealing with doxylamine succinate, dicyclomine hydrochloride, and pyridoxine hydrochloride. Correct?

A. Correct.

* * *

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MR. NACE: Your objection is certainly noted.

BY MR. NACE:

Q. Doctor, let me move on to the McCredie article. You made some reference to the editorial comments of McCredie. What did you mean by that?

A. Well, when I had opened it up -- again, we have been asking about, I as the reviewer, or a peer reviewer, or what I would think that any peer reviewer would ask about. When I saw the title of the article, I was taken aback by it, frankly, "The Innocent Bystander," because that's not usual parlance in any refereed scientific article, as opposed to an editorial, because it is an editorial opinion.

And one of the things that concerned me in the text of it, and I would be affected -- and, I think, again, I would leave it to any reviewer, peer reviewer or not -- that when a scientific article begins by talking about the litigation and that parents -- a quote in the first paragraphs -- "Parents and their lawyers are preparing further lawsuits for some legal opinion," "accepts a list of women who took the drug," and goes on in that nature, that it has already set up a kind of editorial climate. So, I did try, then, after that, of course, to disregard the opening paragraph but did not find the closing paragraph as any surprise.

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MR. WOODSIDE: Objection. Move to strike.

BY MR. NACE:

Q. Is this the kind of language that one usually sees in objective reporting by researchers in the field of epidemiology?

MR. WOODSIDE: Objection.

THE WITNESS: Absolutely not. And it con[trasts] strikingly to the measured language that we have been talking about in most -- of all of this literature that we have reviewed

today.

BY MR. NACE:

Q. This person, McCredie, would you look down at the bottom of the first column. It says, "Janet McCredie, MD, Associate Professor of Radiology." Is there anything in the that article that suggests that McCredie is an epidemiologist, a statistician, a biostatistician?

A. No, there is not.

Q. You made a comment about the article being dispassionate," to use the word that you used. What did you mean by that, and how were you using that word?

A. Well, I think I meant that it seemed to me offputting, far from dispassionate in its introduction and the circumstances in which you try to set up a measured, and

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learned, and objective study to report in a journal, particularly a medical journal.

Q. Were you aware, sir, that Janet McCredie had been listed as an expert witness on behalf of Defendant Merrell?

A. No.

MR. WOODSIDE: Objection.

BY MR. NACE:

Q. Were you aware, sir, that when I attempted to take her deposition --

MR. WOODSIDE: Mr. Nace --

MR. NACE: You wanted to bring up the article by McCredie. We'll bring it up.

MR. WOODSIDE: No, no, no. You brought it up.

MR. NACE: That's right. I'm sure you're going to bring it up in your case, too.

BY MR. NACE:

Q. When I attempted to take the deposition of Dr. McCredie, that she was withdrawn as an expert, and we weren't able to get her deposition?

MR. WOODSIDE: Objection.

THE WITNESS: I have no knowledge of that.

BY MR. NACE:

Q. Let's go to the Aselton article now. If you look down

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at the bottom of the first page, the right-hand column, I think you'll see the name of John B. Chewning, Merrell Dow Pharmaceuticals.

A. Yes.

MR. WOODSIDE: It says "Dr. John B. Chewning" on it.

MR. NACE: It does say "Dr. John B. Chewning, Merrell Dow Pharmaceuticals," who, as I understand it, is also a member of the legal department of the company .

BY MR. NACE:

Q. Do you see that, that he also contributed to this article?

A. They are acknowledging his contribution.

Q. And Dr. Jick is also one of those authors; is that correct?

A. Correct; second author.

Q. Doctor, you had some comment that you wanted to make about this article that you asked to make, and Mr. Woodside objected at the time. What comments did you want to make?

MR. WOODSIDE: I object. That's irrelevant, immaterial, inappropriate, improper.

MR. NACE: I know those are rote objections. But I don't think they are appropriate.

MR. WOODSIDE: They are not rote.

* * *

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conditions. So, metaanalysis, really looking at the way it is used, is really a collection or a view towards aggregating results.

Q. How about pooling?

A. And pooling is often used -- Again, in discourse, some people use the words interchangeably. Some are like Alice in Wonderland: The words are what I say they are. But then there also are very specific statistical techniques that refer to pooling, like when can you put together very different, very precisely defined strata, or stratified analysis. So, I think there has been some rather general and unfortunate use of these phrases.

Q. Why wouldn't you do it in this case?

A. Because here, there is no consistent methodology. That's the problem. Certainly, we would all agree, from the variety of articles that we have reviewed, the techniques, the different populations studied, cohort, case control, if we look

at different risk factors that were considered in some studies, smoking, spermicide, not in other studies, all of these say there is not that kind of uniformity to these studies.

Q. Doctor, you were asked about some Association of Consulting Toxicologists. You are not a toxicologist?

A. No.

UNITED STATES DISTRICT COURT
Western District of Washington at Tacoma

No. C83-74TB

LYNN ANNETTE HILL, et al.,

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MERRELL DOW PHARMACEUTTICALS, INC., et al.,

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Deposition of JAY H. GLASSER, a witness of lawful age, taken on behalf of counsel for the Plaintiffs in the above-entitled matter, pursuant to notice, before Shirley D. Jones, Notary Public, at the law offices of Paulson, Nace & Norwind, 1814 N Street, N.W., Washington, D.C., commencing at 12:27 p.m., Thursday, March 3, 1988.

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[11]
societies that I have belonged to.

Q. Have you held any elected positions in those organizations?

A. Yes, I have.

Q. What would they be?

A. Most recently just a few of them: I was the head of the Social Statistics Section of the American Statistical Association, which that section had some 6,000 members in it as part of the American Statistical Association. I have just completed my duties as the chair of the Statistics Section of the American Public Health Association. And, among other things, I have held several positions as far as grant review committees for national government and similar assignments. Currently, I will be working for the United Nations in an assignment abroad.

Q. I want to ask you about two things, the grant review and also the assignment abroad. What is the assignment abroad that you are talking about?

A. This one that's coming up which, unfortunately, had precluded, if I may mention, my attendance at the trial in Seattle, is to serve for the UN as an expert advisor. This particular project is a six to eight-week first assignment in Pakistan to help them plan a national health interview survey
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and a health examination survey of the entire population of Pakistan. I quickly add, when I say "entire population," meaning that a sample will be drawn from across Pakistan, and people will be asked to come in, interviewed about their health conditions, their health problems, diet, nutritional status, disease states, and also concurrently have a physical and medical exam to look at the medical and clinical aspects of the

problem.

My role in that is three-fold, as I understand it. One is to help analyze some prior, past small studies they have done in preparation to this national survey; secondly, to help them plan the full field implementation, that is to say, the full study itself; and then, thirdly, to help in the training of their personnel. In that sense, I will be giving -- designing and giving several courses which, as we discussed before, include elements of both biometry, epidemiology, and demography, demography being the study of population and distribution of people.

Q. This is through the United Nations?

A. Yes.

Q. How long do you expect to be gone out of the country for that?

A. This will -- The initial assignment, because there may **[13]**
be subsequent ones, will be six to eight weeks.

Q. You mentioned grants. What is your relationship to grants?

A. Well, I have served and am serving as a reviewer for grants. The United States Government, when it gives monies to researchers, calls for those people who are applying to send in research grants. And that's in the way we spoke of before about research design. There would be a protocol for carrying out the study. In order to review these, because these are competitive grants, they call upon what is called peer review. That is that people like myself and others who are working in the cognizant and related fields to review these grants fairly and objectively, to look at both the scientific merit, kind of practical doability, and the possible significance and application of results that would come from these. Through this process of ranking these competitive grants, the awardees are chosen, because usually there are far more applications that come in for the amount of money that's available for these research projects.

Q. Have you also served as a peer reviewer?

A. Yes, I have.

Q. Maybe I'll ask you, first of all -- because we don't know exactly when this tape will be shown. So, what is a peer **[14]**
reviewer?

A. A peer reviewer is where you call upon someone who has commensurate experience and commensurate knowledge to either look at a grant proposal, a research proposal or, in the case of scientific publications and what are are called refereed journals, would be asked to review the submitted article for its validity, reliability, and contribution to the field. So, I have served both as a grant reviewer on research grants, as well as a peer reviewer for journals.

Q. Would you tell us what some of those journals are that you have been a peer reviewer for.

A. The ones that I currently have manuscripts to review, a task that I need to complete before leaving, are the New York State Journal of Medicine, Medical Care, and the American Journal of Public Health.

Q. Have you served in any national or international committees with respect to areas that might be involved with epidemiology?

A. Yes.

Q. Would you tell us what some of those would be.

A. For several years, I have served on committees for the National Center for Health Services Research and Health Care Technology. I have also just served as the chair of a review

* * *

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ever been appointed by a court to do epidemiological analysis?

MR. WOODSIDE: Objection.

MR. NACE: Go ahead.

THE WITNESS: Yes, I have. Recently, I have served as the expert appointed by a court in Richmond, the federal bankruptcy court, in the Dalkon Shield, Robins Dalkon Shield IUD, that is, the intrauterine device litigation that is before the court, which is located in Richmond, Virginia.

BY MR. NACE:

Q. Doctor, let me now try to get to the areas of the relative risk, statistical significance, and that sort of thing. We have over here behind you a board and a new, black Markette pen. . If you feel it is appropriate, I would ask you to use the board at any time. First of all, with respect to relative risk, what is a relative risk as far as epidemiology is concerned

A. I think it would be useful to put some things on the

board. Relative risk, which we can abbreviate as RR, is a concept that is used to appraise the risk of an outcome among an exposed population, where we mean by "exposed population" -- and I'll abbreviate that with POP, with an N, for population. In other words, a group of people who may be exposed to something that we believe -- a drug, a device, or other -- that

* * *

11. Affidavit of John Davis Palmer, Ph.D., M.D. and curriculum vitae (Dock. No. 186), filed Sept. 28, 1989

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UNITED STATES DISTRICT COURT
Southern District of California

No. 84-2013-G(I)

WILLIAM DAUBERT and JOYCE DAUBERT, Individually and as Guardian Ad Litem for JASON DAUBERT, a Minor,
Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES 1 through 50 Inclusive,
Defendants.

NO. 84-2929-G(I)

MICHAEL SCHULLER, ANITA DE YOUNG, and ANITA DE YOUNG as Guardian ad Litem for ERIC SCHULLER,
Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES 1 through 50., Inclusive
Defendants.

[2] **AFFIDAVIT OF JOHN PALMER, M.D.**

1. My name is John Palmer. I am a physician licensed to practice medicine in Arizona, California, and Minnesota. I am a full professor at the Department of Pharmacology, college of Medicine, University of Arizona, Tucson. I received my Bachelor of Science in pharmacy and my Masters in pharmacology from the University of Colorado. I received my Ph.D from the University of Minnesota in pharmacology 1961 and my medical degree from the University of Minnesota in 1962. A copy of my curriculum vitae is attached.

I have served as associate professor of pharmacology and full professor of pharmacology at the University of Arizona. I have also earned a special post-doctoral fellowship; served as a visiting scientist and visiting clinical pharmacologist at the Cardiovascular Research Institute at University of California Medical Center; and have been a visiting lecturer at the University of California, Berkeley where I was also a visiting professor of pharmacology. I have been a visiting scientist and lecturer at the University of Washington School of Medicine, Department of Internal Medicine. I have been a visiting professor of pharmacology at the University of Colorado

Medical Center; a clinical associate professor of medicine at the University of Washington [Boise, Idaho words added by JP] Veterans Administration Hospital; Director of St. Lukes/[V letter added by JP]AMC in Boise, Idaho; [internship word added by JP] held a volunteer position at the Rocky Mountain
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Biological Laboratory; and I have had a major interest in medical education and basic pharmacology.

I have received fellowships from the American Foundation for Pharmaceutical Education, USPHS Combined MD/PhD Training Program, and the USPHR Special Post Doctoral Fellowship. I have received awards for superior scholarship at the University of Colorado, was elected as the outstanding lecturer at the Colorado School of Medicine, and selected to the Dean's List of Excellence in Teaching of Basic Sciences. I have had numerous grants for research and I have served on numerous committees involved with medicine. I have taught Pharmacology, Internal Medicine, Preparation for Clinical Medicine, Clinical Pharmacology of Cardiovascular Drugs, Fluids and Electrolytes, Psychopharmacology, Applied Pharmacology, etc. I have served as a consultant to several Veterans' Administration Hospitals, the Charles F. Kittering Foundation in Denver, Colorado, the National Institutes of Health, and am a member of the American Society for Clinical Pharmacology and Therapeutics, American Society of Pharmacology and Experimental Therapeutics, the American Association for the Advancement of Science, the Western Pharmacology Society, the American Foundation for Clinical Research, etc. I have published approximately 22 articles in scientific journals subject to referee and review, published approximately 7 book chapters and had numerous abstracts published and presented.
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As a pharmacologist I have naturally also had an interest in the actions of drugs and chemicals on the human body and cells. I have performed and have been responsible for animal studies involving drugs. These studies involve determining the

toxic effects of drugs.

2. In teaching pharmacology the subsections that are taught as part of the pharmacology curriculum include toxicology and the subsection of teratology. By virtue of my education, training and experience, I am familiar with the principles and general methodology utilized in determining whether of not a drug is toxic to cells in the humans and have in fact done such research. When one examines whether or not a chemical or drug effects the cells of an fetus one is examining the toxic effects of the substance, a pharmacologic function.

3. I have reviewed various pieces of scientific data and literature pertaining to Bendectin. I have specifically reviewed what I believe to be all of the animal studies pertaining to Bendectin. These include the studies performed by the company bearing the titles 63-01; 63-02; 63-27; 63-28; 63-29; 66-01; 66-02; 66-05; 66-07; 67-12; 75-12; and 75-13.

I have also reviewed original data collected on Bendectin performed by the company that appeared in notebooks 401-T and 458-T. I have also examined reports generated by the manufacturer of Bendectin on animal studies involving drugs other than Bendectin including Thalidomide, Clomid, etc. I

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have further reviewed animal studies that were conducted by research institutions outside the premises of Richardson Merrell. These include studies that are know as the "Roll" studies; the Research Triangle Institute Study; Studies by Hendrickx; Studies by McClure; and others.

I have further reviewed in vitro studies that have been performed pertaining to Bendectin and its component doxylamine succinate. These include studies by the following authors or organizations: Hassell and Horrigan; Budroe; Guntakatta; Crescitelli; and BGA.

I have also examined pharmacological data pertaining to Bendectin and doxylamine succinate. These include various pharmacological articles that I have previously been examined upon in my deposition, which have been provided to the defendant and include Slikker, Holder, Ganes, Scott, and

others.

4. Company data concerning adverse reaction reports, case reports, and other such memoranda are also generally and reasonably relied upon to help determine teratogenicity.

5. I have further examined and reviewed the epidemiological data pertaining to Bendectin. In my opinion, the pharmacological data, the animal studies data, the in vitro studies data, the epidemiological data, and other human data are all, jointly viewed by those who are trying to determine whether or not a drug, such as Bendectin, is teratogenic, although the epidemiological data is the least

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reliable.

6. A component of Bendectin was doxylamine succinate, an antihistamine. It is what is known as a type H_1 class and is clearly associated with Benadryl. It is both a lipophilic and hydrophilic substance and is thereby by definition an antipathic substance. It is moreover of a low molecular weight and is accepted as being able to pass through the placenta and reach the cells of the human fetus.

7. It is my opinion within a reasonable degree of certainty that the pharmacology data shows that Bendectin and specifically its component doxylamine succinate, has teratogenic properties.

8. The animal studies that have been performed show results that found heart defects, reduced fetal size, diaphragmatic hernias, reduced ossification centers (bone composition), sternal defects, limb defects, etc. In fact, the RTI studies produced data that found that there was less than 1 in 1000 chance that Bendectin did not cause ossification defects.

9. It is my opinion within a reasonable degree of certainty that the animal studies performed by the company and those performed by other organizations shows that Bendectin and specifically its component doxylamine succinate, has teratogenic properties.

10. The in vitro studies performed show that Bendectin and doxylamine succinate affected the process of
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chondrogenesis, interfered with DNA synthesis, caused chromosomal breakage and the like.

11. It is my opinion within a reasonable degree of certainty that the in vitro studies performed on Bendectin and its component doxylamine succinate shows that Bendectin and specifically its component doxylamine succinate, has teratogenic properties.

12. It is my opinion within a reasonable degree of certainty that the epidemiological data, company memoranda, case reports, and other human data shows that Bendectin and specifically its component doxylamine succinate, has teratogenic properties.

13. When looking at the evidence in total, it is my opinion within a reasonable degree of medical and scientific certainty that Bendectin is a teratogen and specifically is capable of causing birth defects and limb defects in the human being when ingested at the normal therapeutic dose at the time that the cells of the body are developing and creating numerous structures, including the limbs.

14. I have also examined the medical records pertaining to the Daubert and Schuller children and it is my opinion within a reasonable degree of medical certainty that in each case the drug Bendectin was taken at the period of time such as to effect the cells that would produce the normal limb structure and that Bendectin did cause the limb defects in each of the children.

/s/
John Palmer

Acknowledged before me on this 22nd day of September, 1989.
My Commission Expires: August 15, 1993

/s/
Judy K. Smith, Notary Public

CURRICULUM VITAE

JOHN DAVIS PALMER, Ph.D., M.D.
Department of Pharmacology
College of Medicine
University of Arizona
Tucson, Arizona 85724

June 15, 1987

BIRTH:
Sterling, Illinois
October 31, 1931

EDUCATION:
University of New Mexico, 1949-1951
University of Colorado, 1951-1955, B.S. Pharmacy, M.S. Pharmacology
University of Minnesota, 1955-1962, Ph.D., Pharmacology, 1961; M.S., 1962
Thesis: The Treatment of Experimental Acute Hemorrhagic Hypotension with Mixtures of Pressor Amines.
Director: R.N. Bieter, Ph.D., M.D.

POSITIONS:
Research Assistant, University of Colorado, College of Pharmacy, 1954-55.
Teaching Assistant - Pharmacology, University of Minnesota Medical School, 1955-58.
Fellow, American Foundation for Pharmaceutical Education, 1955-58.
Fellow, USPHS/NIH combined MD/PhD Training Program, 1959-62.
Intern, Internal Medicine, University of Minnesota Hospitals, 1962-63.
Special Postdoctoral Fellow, USPHS/NIH, 1963; awarded but never activated.

Assistant Professor of Pharmacology, University of Colorado Medical Center, 1963-66.
Director, Multidiscipline Laboratories, University of Arizona, College of Medicine, 1966-86.
Associate Professor of Pharmacology, University of Arizona, College of Medicine, 1969-present.
Resident (part-time), Department of Internal Medicine, University of Arizona, College of Medicine, 1972-73, Board Eligible.
Assistant Professor, Internal Medicine (Clinical Pharmacology) University of Arizona, College of Medicine, 1973-present.
Visiting Scientist (Clinical Pharmacology) Cardiovascular Research Institute, University of California Medical Center, San Francisco, July 1973-December 1973 (sabbatical leave).
Visiting Lecturer, University of California, Berkeley, 1973 1980.
Visiting Professor of Pharmacology, University of California, Berkeley, 1975, 1981-present.
Physician-Rotator, Sage Memorial hospital, Navajo National Health Foundation, Ganado, AZ, September, 1983.
Visiting Scientist, Lecturer, University of Washington School of Medicine, Department of Internal Medicine, Veterans Administration Medical Center, Boise, Idaho, 1984-85, sabbatical leave.
Visiting Professor of Pharmacology, University of Colorado Medical Center, Denver,colorado, October 1985, October 1986, February 1987, and October 1987.
Clinical Associate Professor of Medicine, University of Washington Veterans Administration Hospital, Boise, Idaho, January 1986 through December 1986.
Director, St. Luke's/VMAC, Boise, Idaho, Preliminary Year Internal Medicine Residency, 1986.
Volunteer Physician, Rocky Mountain Biological Laboratory, Gothic, Colorado, Summer, 1986, 1987 and 1988.

Professor of Pharmacology, university of Arizona, college of Medicine, 1988.

MEDICAL LICENSURE AND CERTIFICATION:

Minnesota, 1963, Examination
Arizona, 1971, Reciprocity
California, 1973, Examination/Reciprocity
American Board of Internal Medicine - Eligible

MAJOR INTEREST/SPECIALIZATION:

Medical Education
Basic Pharmacology
Cardiovascular
Antibiotics and Chemotherapy
Shock
Clinical Pharmacology
Rational use of drugs in humans
Drugs for the elderly

FELLOWSHIPS AWARDS AND GRANTS:

Fellowships:

American Foundation for Pharmaceutical Education, 1955-58.
USPHS Combined MD/PhD Training Program, 1959-62.
USPHS Special Postdoctoral Fellowship, 1963, awarded but not activated.

Awards:

Cited for Superior Scholarship, University of Colorado, 1954
Dean's List for Excellence in Teaching of Basic Sciences.
Committee on Faculty Tenure and Promotion, Chairman, temporarily then member, College,
Selected as Outstanding Lecturer (small group leader) University of Colorado School of Medicine, Fall Quarter, 1985 and 1986.

Grants:

Principal Investigator:

Effect of Endotoxin on Vascular Control Mechanisms, NIH 1964-67 and GRS, University of Colorado, 1954-65.

Vascular Changes Associated With the Development of Cardiogenic Shock, American Heart Association, 1966-68.

Neutralization of Endotoxin by Antibiotics, GRS 1970-72.

Neutralization of Endotoxin by Antibiotics, Arizona Heart Association, 1970, sponsorship of Summer medical Student Research (two students).

Effect of Glucocorticoids on Cardiovascular Function, American Heart Association, 1970-72.

A Model of IgE Induced Pathophysiology Following Aerosol Antigen Challenge BRS, 1977-79, with Dr. M. Halonen.

Effect of Glucocorticoids on Vascular Reactivity. UpJohn, 1978-1981.

Co-Principal Invetigator:

IgE Induced Cardiovascualr Pulmonary Alterations with R.N. Pinckard, Ph.D. Arizona Heart Association, 6/1/73-5/31/75.

Collaborating Investigator:

Diagnosis and Characterization of Myocardial Infarction with R.N. Pinckard, Ph.D., NHIL, 7/01/71-6/30/74.

Factors Controlling Humoral Antibody Synthesis with R.N. Pinckard, Ph.D., NIAID, 7/01/71-6/30/77/

Intensive Surveillance of Drug User in and Inpatient Population of a Hospital General Medical Ward : th R. Bressler, M.D., FDA contract, 7/01/73-6/30/77.

Clinical Pharmacology Research Training Grant, with R. Bressler, M.S., NIH 1975-present.

Pulmonary and Circulatory Alterations Induced by IgE with M. Halonen, Ph.D., PHS, 12/01/77-11/30/91, HL22582, $77,681.

Autonomic Alterations in IgE Producing Rabbits, with M. Halonen, Ph.D., and H. Yamamura, Ph.D., PHS, 12/01/83-11/30/86, HL31219.

Myocardial Damage and Fibrinolytic Agents, with J. Corrigan, M.D. and H. Allen, M.D., Arizona Heart Association and BRSG, 1982-1983.

Effects of IgG on IgE Induced Allergic Reactions with M. Halonen, Ph.D., Arizona Lung Association, 7/01/77-6/30/78.

Development and Evaluation of Instrument Systems for Non-invasive Detection, Characterization and Quantification of Atherosclerotic Lesions. I: Development of New X-ray Contrast Media, with Drs. T. Ovitt, D. Carter and S,. Nundleman. HF72931, 9/77-9/80.

Molecular Pathology of PAFs, Subgrant to University of Arizona with R.N. Pinckard, Ph.D., University of Texas at San Antonio and M. Halonen, Ph.D., University of Arizona. 4/01/78-3/31/91.

COMMITTEES:

Admissions Committee, Chairman, College of Medicine, 1966-69 and Member, 1978-81.

Group on Student Affairs, Association of American Medical Colleges, Member, National and Regional, 1966-69.

Association of American Medical Colleges, Committee on Financial Assistance to Medical Students, Member, National, 1968-69.

Committee on Human Research, Medical Referee Panel, Member, University.

Human Subjects Committee, Member, University, 1972-76.

Committee on Scholarships and Awards, Member,

University, 1968-70.
Financial Assistance Committee, Chairman, College, 1968-69.
Academic Policy and Procedures Committee, Member, College, 1968-69.
Minority Groups in Health Sciences, Member, College, 1968-75.
Interim Curriculum Committee, Member, College, 1968-69.
Pharmacology Search Committee, Member, College, 1968-70.
Ad Hoc committee on Audiovisual Services, Chairman, College, 1969-70.
Exhibits Committee, US-Mexico Border Public Health Association, Member, International,
Medical Education Review Committee, Physical Education Branch, Division of Health Professions Education, National Institutes of Health DHEW, Member, National, 1971-73.
Pharmacy and Therapeutics Committee, Veterans Administration Hospital, Member, 1966-present, Chairman, 1974-1976. Arizona Medical Center, Member 1971-present, Chairman, 1975-1984.
Ad Hoc Advisory Committee to Curriculum Committee, Member, College, 1974-75.
Preparation for Clinical Medicine, Member, College, 1975-77.
Committee on Graduate Study, Member, University 1976-78.
Clinical Research Unit Advisory Committee, 1977-1981. 81.
Phase III Electives, Member, College of Medicine, 1978-80.
Nominating Committee, Member, College of Medicine, 1981-84; Chairman, 1983-1984.
Education and Professional Training Committee, Long-Term Care Gerontology Center, University of Arizona, 1981-1986.

Committee on Geriatrics, College of Medicine, 1980-1986.

TEACHING RESPONSIBILITIES:

Pharmacology 501/801, Course Coordinator, 1968-1970 and 1976-present. Sections taught: Cardiovascular, Antibiotics and Chemotherapy, Alcohol, General Principles, Anticoagulants and Vitamins, 1968-present. 120 hours, 120 medical and graduate students. Course elected as the Outstanding Basic Science Course, 1981, 1983, and 1986.
Internal Medicine 503, Basic Clerkship, 1974-present. Ward attending, 2-3 months per year, plus 3-4 months per year on the Geriatric Assessment Unit.
Preparation for Clinical Medicine, Physical Diagnosis, 1 semester per year, 1975-present.
Phase III Electives, Clinical Pharmacology of Cardiovascular Drugs, Fluids and Electrolytes, and Clinical Pharmacology Clerkship, 1973-present.
POOL 654, Psychopharmacology. Clinical Use of the Major Psychopharmacologic Drugs. 2 hours, 50 students, 1983.
POOL 372. Applied Pharmacology. Antibiotics, 6 hours, 100 nursing students, 1983.
POOL 554. Cardiovascular Pharmacology, Antihypertensive Drugs and Antiarrhythmic Drugs, 3 hours, 10 graduate students, 1979-present.
Core Curriculum for Psychiatry Residents, Alcohol, 3 hours, 5 residents, 1986.
POOL 208. University of California - Berkeley, Course Director, 1975 and 1981-present.

CONSULTATION:

Veterans Administration Hospital, Denver, Colorado, 1964-66.
Veterans Administration Hospital, Tucson, Arizona, 1966-present.
Charles F. Kettering Foundation, Denver, Colorado, 1967.
Bureau of Health Manpower Education, Division of Physician and Health Professions Education, Department of Health, Education and Welfare, National Professions Education, Department of Health Education and Welfare, National Institutes of Health, Bethesda, Maryland, 1971.
Department of Health, Education and Welfare, Region IX, Bureau of Health Resources Development, 1973-79.
Department of Health, Education and Welfare, Health Resources Administration, Bureau of Health Manpower, 1978-79, Financial Distress Review and AHEC Review.
PHS, Health Resources Administration, Bureau of Health Professions, 1980-81.
Gibson-Stephens Neuropharmaceuticals, 1984.

MEMBERSHIPS:

American Society for Clinical Pharmacology and Therapeutics.
American Society for Pharmacology and Experimental Therapeutics, by election.
American Association for Advancement of Science, fellow, by election.
Western Pharmacology Society.
Health Sciences Communication Association.
Association of Directors of Multidiscipline Laboratories.
American Federation for Clinical Research.

SUPERVISION OF GRADUATE STUDY:

David B. Bell, University of Colorado School of Medicine, Ph.D., M.D., Director, Private Practice of Pediatrics.
V. Gene Erwin, University of Colorado School of Medicine, Ph.D., Committee Member, Dean, University of Colorado, College of Pharmacy.
Richard J. Kraemer, University of Colorado School of Medicine, Ph.D., Committee Member, Associate Professor of Pharmacology and Assistant Dean, University of Colorado, College of Pharmacy.
Marilyn Halonen, University of Arizona, College of Medicine, Ph.D., (Microbiology) Committee Member, Associate Professor, University of Arizona College of Medicine.
Sheldon Schuester, University of Arizona, College of Medicine, Ph.D., (Biochemistry), Committee Member, Faculty, University of Nebraska School of Medicine.
Aniko Meng, University of Arizona, College of Medicine, Ph.D. (Microbiology), 1978.
Anthony F. O'Malley, M.D., University of Arizona, College of Medicine, Committee Member, Ph.D., Candidate, (Pharmacology).
Sally Betz, Ph.D., (Microbiology), 1978.
Michael Wandell, Pharm. D., Postdoctoral Fellow, Clinical Pharmacology, 1980.
William Banner, M.D., Ph.D., Pharmacology, Committee Member, 1981.
Cindy Blackwell, M.S., (Toxicology), 1983.
Steven Fischer, Predoctoral Student, Microbiology, Committee Member.
J. Womble, Ph.D., Pharmacology, Committee Member, 1981.
Anne Weisse, M.S., Toxicology.
Leslie Sebring, Pharmacology, Committee Member, Ph.D., 1986.

PUBLICATIONS:

Articles in Scientific Journals
Subject to Referee Review:

Palmer, J.D., and Bieter, R.N. The treatment of experimental acute hemorrhagic hypotension with mixtures of pressor amines. Minn. Med. Bull. 33:301, 1962.

Bernstein, E.F., Palmer, J.D., Aaberg, T.A. and Davis, R.L. Studies on the toxicity of hypaque-90 percent, following rapid intravenous injection. Radiol. 76:88, 1961.

Rifkind, D. and Palmer, J.D. Neutralization of endotoxin toxicity in chick embryos by antibiotics. J. Bact. 92:815, 1967.

Palmer, J.D. Multidiscipline Laboratories. Arizona Medicine. 24:820, 1967.

Pinckard, R.N., Olson, M.S., O'Rourke, R., Palmer, J.D., Kelley, R.E. and Goldfein, S. Development of complement-fixing 19S, antiheart mitochondria autoantibody, following myocardial infarction in dogs. Circ. Res. 29:276, 1971.

Palmer, J.D., Olson, M.S., O'Rourke, R.A., Pinckard, R.N. and Goldfein, S. Experimental myocardial infarction. American Heart J. 81:729, 1971.

Pinckard, R.N., Olson, M.S., Kelley, R.E., DeHeer, D.H., Palmer, J.D., O'Rourke, R.A. and Goldfein, S. Antibody-independent activation of human C1 after interaction with heart subcellular membranes. J. Immunology 110:1376, 1973.

Palmer, J.D. and Bressler, R. Drug-Drug Interactions. Contemporary Ob/Gyn. 2(3):86, 1974 (by invitation).

Palmer, J.D., and Rifkind, D. Neutralization of the Hemodynamic Effects of Endotoxin by Polymyxin B. Surgery. Gynecology & Obstetrics 138:755, 1974.

Palmer, J.D., Pinckard, R.N., Halonen, M., Butler, C. and O'Rourke, R.A. IgE Induced Cardiopulmonary Changes in the Conscious Adult Rabbit (submitted for publication).

Pinckard, R.N., Halonen, M., Palmer, J.D., Butler, C., Shaw, J. and Henson, P.M. Intravascular Aggregation and Pulmonary Sequestration of Platelets During IgE-Induced Systemic Anaphylaxis in the Rabbit. Abrogation of Lethal Anaphylaxis by Platelet Depletion. J. of Immunology. 119"2185, 1977.

Palmer, J.D. Clinical Uses of Warfarin. Drug Therapy, 11"119, 1981.

Halonen, M., Palmer, J.D., Lohman, I.C., McManus, L.M. and Pinckard, R.N. Respiratory and Circulatory Alterations Induced by Acetyl Glyceryl Ether Phosphorycholine (AGEPC), A Mediator of IgE Anaphylaxis in the Rabbit. Am. Rev. Resp. Dis. 122:915, 1980.

Halonen, M., Palmer, J.D., Lohman, I.C., McManus, L.M. and Pinckard, R.N. Differential Effects of Platelet Depletion on the Physiologic Alterations of IgE Anaphylaxis and Acetyl Glyceryl Ether Phosphorylcholine Infusion in the Rabbit. Am Rev. Resp. Dis. 124:416-421, 1981.

Nugent, C.A., Palmer, J.D., and Ursprung, J.J. Guanadrel Sulfate Compared with Methyl-dopa for Mild and Moderate Hypertension. Pharmacotherapy 2:378. 1982.

Palmer, J.D., Nugent, C.A. Guanadrel Sulfate: A Postganglionic Sympathetic Inhibitor for the Treatment of Mild to Moderate Hypertension. Pharmacotherapy, 3:220-229, 1983.

Palmer, J.D., Clinical Pharmacology and CNS Effects of Guanadrel Sulfate and the Major Classes of Anti-hypertensive Agents. Health Science Review 1:5-7, 1984.

Smith, P.F., Palmer, J.D., Homes, T. and Halonen, M. The Responsiveness of Rabbit Bronchial Rings to Antigen. Immunopharm. 12:89-96, 1986.

Bloom, J., Baumgartner-Folkerts, C., Palmer, J., Yamamura, H., and Halonen, M., A Muscarmic Receptor Subtype Modulates Vagally Stimulated Bronchial Contraction. J. Appl. Physiol., 1988, in press.

Book Chapters:

Bressler, R. and Palmer, J.D. Drug Interaction in Aging. In: Drug Issues in Geropsychiatry, pp. 49-60. Edited by Fann, W.E. and Maddox, G.L., Baltimore, MD, Williams and Wilkins, 1974.

Palmer, J.D. A medical educator looks at pharmacy in the future. American Association of Colleges of Pharmacy and National Associations of Boards of Pharmacy Dist. 8, Proceedings of the 26th Annual Meeting. p.17, 1967 (by invitation).

Palmer, J.D. Drug Therapy for the Elderly. Bressler, R. and Conrad, K. Eds. Mosby, 1982. (Therapy for Cardiovascular Disorders and Anticoagulant Drugs.)

Palmer, J.D. and Conrad, K.A. Cardiovascular Drugs and the Management of Heart Disease. Ewy. G. and Bressler, R. Eds. Raven, 1982. Anticoagulant Drugs.

Griffith, W. Complete Reference to Prescription and Non-Prescription Drugs. Technical Consultants, John D. Palmer and William Jones. H.P. Books, Tucson, Arizona, 1983.

Palmer, J.D. and Conrad, K.A. Current Cardiovascular Drug Therapy. Ewy, G. and Bressler, R. Eds. Raven 1984. Anticoagulant Drugs: Heparin and Warfarin.

Abstracts Published and Presented:

Rifkind, D. and Palmer, J.D. The Neutralization of Endotoxin by Antibiotics Bactl. Proc. April, 1966. Am. Society for Microbiology.

Palmer, J.D. Effect of Phenoxybenzamine on the Reactivity of Resistance and Capacitance Vessels During Endotoxin Shock. Pharmacologist 8:173, 1966.

Palmer, J.D., Rifkind, D., Beauchamp, R. and Cotner, R. Neutralization of the Hemodynamic Effects of Endotoxin by Polymyxin B. Pharmacologist 13:299, 1971.

Palmer, J.D., Pinckard, R.N., Halonen, M., O'Rourke, R.A. and Butler, C. Anaphylactic Shock Related to Acute Pulmonary Hypertension. American Heart Association Meeting, November, 1975. Circ. 52(2):88, 1975.

Halonen, M., Palmer, J.D., Butler, C., Henson, P.M. and Pinckard, R.N. Role of the Platelet in IgE-Induced Systemic Anaphylaxis in the Rabbit. Fed. Proc. 36:1329, 1977.

Halonen, M., Smith, P., Holmes, T., Cutcher, A., and Palmer, J. Contraction of Rabbit Bronchial Rings to Antigen, Acetyl Glyceralether Phosphorylcholine and Histamine. Submitted, FASEB (ASBC/AAI) 1984.

Baumgartener, C., Bloom, J.W., Yamamura, H.I., Palmer, J.D., and Halonen, M. Pirenzepine Preferentially Inhibits Bronchial Contraction Induced by Pre- vs. Post-ganglionic Parasympathetic Nerve Stimulation. Submitted, American Thoracic Society, December, 1986.

Halonen, M., Baumgartener, C., Bloom, J.W., Palmer, J.D., and Yamamura, H.I. Effects of Histamine on Neuronally Induced Contraction of Rabbit Mainstem Bronchus. Submitted, American Thoracic Society, December, 1986.

Dunn, A.M., Palmer, J.D. and Halonen, M. A Search for the Mediators Responsible for Antigen-Induced Contraction of Peripheral Lung Strips (PLS) from IgE-producing Rabbits. Submitted, American Thoracic Society, December, 1986. -

Palmer, J.D., Halonen, M.J., Blackwell, C.L. In Vitro Characterization of Vascular Smooth Muscle Responses and Mediators in Rabbit IgE Anaphylasis.

Dunn, A.M., Palmer, J.D. and Halonen, M.J. Platelet Activating Factor (PAF) and Histamine Mediate Antigen-Induced Contraction of Rabbit Peripheral Lung Strips. Submitted, FASEB (AAI), December, 1987.

Palmer, J.D., Blackwell-Dyke, C., Wiese, A.J.C. and Halonen, M.J. In Vitro Characterization of Mediators Causing Pulmonary Artery Constriction in Rabbit IgE Anaphylasis. Submitted, FASEB (ASPET), December 1987.

Quan, S.F., Baumgartener-Folkerts, C., Trombley, J., Sobonya, R.E., Halonen, M.J. and Palmer, J.D. Influence of Airway Epithelium Removal on the Relationship Between in Vivo and In Vitro Histamine Responsiveness in Rabbits. Submitted, FASEB (ASPET), December, 1987.

Halonen, J., Dunn, A.M., Palmer, J.D. and McManus, L.M. An Anatomic Basis for the Species Difference in Responses of Guinea Pig and Rabbit Peripheral Lung Strips to Platelet Activating Factor. Submitted, American Thoracic Society, November, 1987.

Halonen, M., Baumgartener-Folkerts, C., Palmer, J.D. and Bloom, J.W. Airway Responsiveness to Methacholine in IgE-Producing Rabbits. To be presented, American Academy of Allergy and Immunology, March, 1988.

Abstracts Published:

Palmer, J.D. Effect of Endotoxin Shock on Mechanisms Regulations Net Transcapillary Fluid Exchange. Clin. Res. 14:128, 1966.

Bell, D.B. and Palmer, J.D. Peripheral Vascular Changes Associated with Experimental Coronary Embolization. Circ. 34(3):53, 1966.

Palmer, J.D. Effect of Endotoxin on Mechanisms Regulating Net Transcapillary Fluid Exchange. European Conf. on Microcirculation, 4th, 1966, p.47. Abstracts ..(Cambridge, 1966) 134P.

Pinckard, R.N., Olson, M.S., O'Rourke, R.A., Palmer, J.D. and Goldfein, S. Mitochondrial Autoantibody Induced by Myocardial Infarction. Clinical Research 19:118, 1971.

O'Rourke, R.A., Pinckard, R.N., Olson, M.S., Palmer, J.D. and Goldfein, S. Myocardial Autoantibody Due to Myocardial Injury. American J. Cardiology 26:652, 1970.

Pinckard, R.N., Olson, M.S., DeHeer, D.H., O'Rourke, R.A., Palmer, J.D. and Goldfein, S. Identification of a heat-labile, IgM Anti-Heart Mitochondria Autoantibody in Human Sera. Fed. Proc. 31:658, 1972.

Palmer, J.D., Pinckard, R.N., Halonen, M., Butler, C. and O'Rourke, R.A. IgE Induced Cardiopulmonary Changes in the Conscious Adult Rabbit. Clin. Res. 23:83A, 1975.

Halonen, M., Palmer, J.D., Butler, C., Henson, P.M. and Pinckard, R.N. Role of the Platelet in IgE Induced Systematic Anaphylaxis. Fed. Proc. 36:1329, 1977.

Halonen, M., Stanfield, M. and Palmer, J.D. Role of Histamine in IgE Induced Systemic Anaphylaxis in the Rabbit. Fed. Proc. 38:1415, 1978.

Halonen, M., Palmer, J.D., Lohman, I.C., Hanahan, D.J. and Pinckard, R.N. Cardiovascular and Respiratory Alterations Induced by Acetylglycerol Ether Mediator (AGEM) in Platelet Depleted Rabbits. Fed. Proc. 39:905, 1980.

12. Excerpts from "Reproductive Health Hazards in the Workplace, Congress of the United States, Office of Technology Assessment (Ex. 43 to Pltfs.' Opp. to Summ. Judg.), filed Aug. 28, 1989

Reproductive Health Hazards in the Workplace

OTA Reports are the principal documentation of formal assessment projects. These projects are approved in advance by the Technology Assessment Board. At the conclusion of a project. The Board has the opportunity to review the report, but its release does not necessarily imply endorsement of the results by the Board or its individual members.

CONGRESS OF THE UNITED STATES
[SEAL] Office of Technology Assessment
Washington, D.C.

[167]

Toxicology Studies

Toxicology studies include in vitro and whole animal tests of suspected hazards that allow the investigator to examine the roles of dose and routes of exposure. While extrapolation to humans is a complicated task, these studies, properly executed and interpreted can *predict* an association with agents to which humans are exposed, in contrast to epidemiology studies in which the humans will already have been affected by exposure to the hazard.

Although evidence from studies on humans is often used to refute or confirm results from animal screening tests, toxicology studies are necessary for several reasons (20):

- Experimental studies that deliberately expose humans to potentially toxic chemicals are ethically unacceptable, except in special circumstances (e.g., clinical trials for new pharmaceuticals) where there is extensive evidence from animal studies and informed consent has been given.
- Epidemiological studies of workers exposed to a chemical already in production, or reports of adverse reactions to substances, are available for only a small number of chemicals (see chapter 4).
- Even in epidemiological studies of exposed humans, results are difficult to interpret because of factors such as the lack of large enough samples and good exposure data, difficulty in measuring endpoints, and confounding variables.
- Although epidemiological studies are variable, tests on animals have proven to be an important source of data on human risk.

* * *

[169]

A basic tenet of toxicology is that effects observed in experimental animals can be used to infer likely effects (or lack of effects) in humans, with appropriate consideration of biological differences between species. And, in general animal models do have good predictive value for humans (see chapter 4). For example, in reproductive toxicology studies, substances that affect menstrual cycles in monkeys and estrous cycles in rodents also affect menstrual cycles in humans (tables 6-4 and 6-5). Effects on fertility in rodents also seem to be a good indicator of effects in

humans; most of the original work on contraceptive agents was carried out on rodents (1). However, interpreting effects of toxic doses on sexual behavior and pregnancy from animals to humans is far more complex. There are so many differences in sexual behavior between humans and animals that special care must be exercised not to misinterpret results.

Selection of the proper species is extremely important because one or even more species may give "false negative" results. The experience with Thalidomide is a case in point. Effects similar to the phocomelic-type limb deformity observed in humans were observed in a few breeds of rabbits and several species of primates. Thalidomide has been tested in 10 strain of rats, 15 strains of mice, 11 breeds of rabbits, 2 breeds of dogs, 3 strains of hamsters, 8 species of primates, and in cats, armadillos, guinea pigs, swine and ferrets. Developmental effects were only occasionally produced in any of these species. However, there were fertility effects: prenatal mortality was high in rabbits, and there was a low conception rate in rats (20). This underscores the importance of selecting the appropriate species examining other endpoints as indicators of toxic effects, and of performing human epidemiology studies to corroborate the information from animal studies.

Table 6-4 — Selected Examples of Reproductive Toxic Effects Common to Animals and Humans

Compound	Effect in animals	Effect in humans
Benzene	Estrous cycle disturbance, rat	Menstrual disorders
Styrene	Estrous cycle disturbance, rat	Menstrual disorders
Chlordecone (Kepone)	Testicular atrophy, decreased fertility, mouse, rat, rabbit, both sexes, females more affected	Decreased sperm count and motility, abnormal morphology
Chloroprene	Testicular damage, decreased sperm count, dominant lethal mutations, mouse, rat, cat	Decreased libido, impotence, decreased sperm count, motility, abnormal morphology, increased spontaneous abortion in wives
DBCP	Testicular atrophy, decreased fertility, dominant lethal mutations, rat, rabbit, guinea pig	Testicular atrophy, decreased sperm count, decreased fertility
Arsenic	Embryolethal, teratogenic, mouse, hamster, rat	Low birth weight, spontaneous abortions
Carbon monoxide	Fetotoxic, low birth weight, poor postnatal development and brain damage, rodent, rabbit, sheep, pig, monkey	Fetotoxic, low birth weight, fetal brain damage
PCB	Low birth weight, high perinatal and postnatal mortality, poor postnatal growth, skin discoloration, mouse, rat, rabbit, pig, dog, monkey Prolonged estrous cycle, rat Prolonged menstrual cycle, donkey Spontaneous abortion, rhesus monkey	Low birth weight, high postnatal mortality, skin discoloration Menstrual disorders
Lead	Wide spectrum of effects, rats and mice, both sexes	Wide spectrum, both sexes
EDB	Sterility, rats, bulls	Reduced fertility in men
Carbon disulfide	Effects on spermatogenesis, rats Early embryonic mortality — increased congenital malformations, rat	Sperm abnormalities Spontaneous abortions, women

[illegible] Chemical Hazards to Human Reproduction (Park Ridge, NJ: Noyes Data Corp., 1983), p. 184.

BEST AVAILABLE COPY

13. "Report on the Safety of Bendectin/Diclectin for Use in the Management of Nausea and Vomiting of Pregnancy," dated Aug. 11, 1989 (submitted in support of Merrell Dow's Reply to Affidavits of Pltfs.' Experts Submitted in Opp. to Deft.'s Mot. for Summ. Judg.), filed Oct. 3, 1989

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Attorneys for Defendant,
MERREL DOW PHARMACEUTICALS INC.

UNITED STATES DISTRICT COURT
For the Southern District of California

NO. 84-2013-G(I)

WILLIAM DAUBERT; JOYCE DAUBERT, Individually and as Guardians Ad Litem for JASON DAUBERT, a minor,
Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES 1 through 50, Inclusive,
Defendants.

NO. 84-2929-G(I)

MICHAEL SCHULLER, ANITA DE YOUNG, and ANITA DE YOUNG as Guardian Ad Litem for ERIC SCHULLER,
Plaintiffs,

v.

MERRELL DOW PHARMACEUTICALS, INC., and DOES
1 through 50, Inclusive

Defendants.

DEFENDANT'S REPLY TO AFFIDAVITS OF PLAINTIFFS' EXPERTS SUBMITTED IN OPPOSITION TO DEFENDANT'S MOTION FOR SUMMARY JUDGMENT

REPORT ON THE SAFETY OF BENDECTIN/DICLECTIN FOR USE IN THE MANAGEMENT OF NAUSEA AND VOMITING OF PREGNANCY

Prepared by a panel of consultants in teratology for the Special Advisory Committee on Reproductive Physiology to the Health Protection Branch.

11 August 1989

INTRODUCTION

Diclectin is the only drug product on the Canadian market that is indicated specifically for the management of nausea and vomiting of pregnancy. It contains the same active ingredients as Bendectin. Bendectin was marketed for many years worldwide by Merrell Dow.

Recently, controversy regarding alleged association of Diclectin with birth defects has been raised in the Canadian parliament. The Minister of Health and Welfare Canada has requested an independent review by an expert panel. The following report is respectfully submitted.

REPORT

The evaluation of Bendectin (doxylamine succinate; pyridoxine hydrochloride) teratogenicity has included extensive human

epidemiological studies, whole animal studies, and in vitro studies involving several methods. There has been no prescription drug that has been more extensively studied for reproductive toxicity. After considering five parameters for evaluating teratogenicity, it can be concluded that the prescribing of Bendectin to a human population presents no measurable reproductive risks to that population. These parameters include:

1. Human epidemiological studies evaluating the association of birth defects and Bendectin exposure.

2. Evaluating the changing incidence of birth defects with changing use of Bendectin (secular trend data).

3. Animal test results.

4. Dose-response relationship of animal tests.

5. Biological plausibility.

Controlled studies involving over 130,000 patients have not demonstrated any reproducible or consistent association of birth defects with Bendectin exposure. In fact, the results of the epidemiological studies are just what one might expect of an agent without reproductive or teratogenic risks.

Secular trend data from several sources do not support an association between Bendectin exposure and the incidence of birth defects. The frequencies of the limb reduction defects (LRD) and congenital heart disease (CHD), specifically, are not correlated with Bendectin exposure; after withdrawal of the use of Bendectin in the United States, there was no decrease in their rates of occurrence.

Animal studies in primates (Hendrickx et al, 1985) and extensive studies in rats sponsored by the U.S. Food and Drug Administration (Tyl et al, 1988) demonstrate the lack of teratogenicity of Bendectin at many times the human therapeutic dose. There are no peer reviewed or responsibly performed studies that demonstrate a teratogenic effect of Bendectin in any animal species.

Of course, a dose-response relationship is not present in animal models since teratogenicity is not produced in the pharmacological range in which the drug is used.

The allegation of teratogenicity is not supported by in vitro studies that have tested doxylamine at doses above the levels reached in humans receiving therapeutic doses of Bendectin. These investigations have examined the toxicity of doxylamine using mutagenesis testing and toxicity in various cell culture systems. Furthermore, after more than thirty million women have been treated for nausea and vomiting of pregnancy and after numerous studies to evaluate the reproductive effects of Bendectin, there is no indication that there is a spectrum of malformations associated with Bendectin exposure - a so-called Bendectin Syndrome - as there is with all other proven human teratogens.

This analysis allows us to conclude that Bendectin presents no measurable reproductive risk.

In recent years, methods for assessing the combined outcome of a number of related studies have been developed. This methodology, termed meta-analysis, has been applied to the human studies regarding Bendectin. The meta-analysis of the pooled results of 17 trials indicates no statistically significant relationship between maternal Bendectin exposure during the first trimester of pregnancy and subsequent fetal abnormalities (Einarson et al, 1988).

There is a high incidence of birth defects in the general population, even in those women who take no drugs. Bendectin has not altered this incidence. The meta-analysis yields an odds ratio of 1.01 with a 95% confidence interval of 0.66 to 1.55. This means that the range of possibilities for the risk of congenital malformation associated with exposure to Bendectin is between two-thirds and one-and-one-half times the risk of malformation that occurs in the general population. When a confidence interval includes unity, it indicates no increased risk.

After consideration of the relevant data, the panel submits the following recommendations in response to the Minister's questions.

Q1. Given available date, is there evidence that exposure to Bendectin/Diclectin during pregnancy increases the risk of congenital malformations in the offspring?

A. No. Numerous studies in animals and in humans that have been reported in the scientific and medical literature demonstrate that Bendectin is not a teratogen. A compound that has no teratogenic effect can be expected, solely on the basis of chance, to be associated with congenital malformations if it is used widely by pregnant women. The types of congenital malformations reported will vary considerably, not following a consistent pattern of birth defects. The safety of Bendectin/Diclectin in the management of nausea and vomiting of pregnancy has been established by its use in many thousands of pregnant women. The types and numbers of abnormal offspring born to these women were in no way different from those that would be expected to occur in a similar group of women who did not take these drugs during pregnancy. The panel believes that the risks of Bendectin have been grossly misrepresented to the public.

Q2. Does Bendectin/Diclectin serve a useful role in the management of nausea and vomiting of pregnancy?

A. Yes. These drugs were the only ones for which sufficient evidence of safety and effectiveness in the management of nausea and vomiting of pregnancy was submitted to drug regulatory bodies in Canada and abroad, thereby allowing this claim to be made. No other drugs have been nearly so well investigated for this purpose. It must be emphasized that Bendectin was never banned from sale in any country. It was withdrawn from the market worldwide in 1983 by the manufacturer who found the legal costs of defending its use (successfully in the majority of cases) to be prohibitive.

There has been an unfortunate consequence of this withdrawal for pregnant women. For example, in the United States, the number of women being admitted to

hospital suffering from severe nausea and vomiting of pregnancy has increased two-fold.

Q3. Does the benefit [t]o risk assessment of Diclectin indicate that it should be removed from sale in Canada?

A. No, for the reasons cited above. It would be a disservice to Canadian women to withdraw this drug from the market.

Q4. If the answer to question three is no, what restrictions, if any, should be placed on the sale of Diclectin? Are any changes needed in the physician or patient labelling?

A. There should be no restrictions placed on the availability of Diclectin in Canada. It should be indicated for the management of nausea and vomiting of pregnancy without the qualifications which exist at present. The panel believes that there is an overemphasis on cautionary statements in the current labelling for Diclectin, which is not reflected in recent studies that have been reported in the medical and scientific literature. The labelling should be modified accordingly.

REFERENCES

1. Hendrickx AG, Cukierski M, Prahalada S, Janos G, Booher S, and Nyland, T: Evaluation of Bendectin embryotoxicity in nonhuman primates: II. Double-blind study in term cynomolgus monkeys. Teratology 32:191-194, 1985.

2. Tyl RW, Price CJ, Marr MC, and Kimmel CA: Developmental toxicity evaluation of Bendectin in CD rats. Teratology 37:539-552, 1988.

3. Einarson TR, Leeder JS, and Koren G: A method for meta-analysis of epidemiological studies. Drug Intelligence and Clinical Pharmacy 22:813-824, 1988.

4. Biringer A: Antinauseants in pregnancy: teratogens or not? Canadian Family Physician 30:2123-2125, 1984.

PANEL

Dr. Robert L. Brent, Philadelphia, Pennsylvania
Dr. Gideon Koren, Toronto, Ontario
Dr. Anthony Scialli, Washington, D.C.
Dr. Ernest Zimmerman, Cincinnati, Ohio

REPRESENTATIVE FROM THE HEALTH PROTECTION BRANCH

Dr. Michele Brill-Edwards (Chair for the Panel)

REPRESENTATIVES FROM THE SPECIAL ADVISORY COMMITTEE ON REPRODUCTIVE PHYSIOLOGY

Dr. Jack H. Walters (Chairman of the Committee)
Dr. Carl E. Boyd (HPB) (Executive Secretary of the Committee)

APPENDIX TO THE REPORT ON THE SAFETY OF BENDECTIN/DICLECTIN FOR USE IN THE MANAGEMENT OF NAUSEA AND VOMITING OF PREGNANCY

CURRICULA VITAE OF THE EXPERT PANEL

Dr. Robert Brent (to follow)
Dr. Gideon Koren (to follow)
Dr. Anthony Scialli
Dr. Ernest Zimmerman

REFERENCE PAPERS CITED IN THE REPORT OF THE PANEL

1. Hendrickx AG, Cukierski M, Prahalada S, Janos G, Booher S, and Nyland, T: Evaluation of Bendectin embryotoxicity in nonhuman primates: II. Double-blind study in term cynomolgus monkeys. Teratology 32:191-194, 1985

2. Tyl RW, Price CJ, Marr MC, and Kimmel CA: Developmental toxicity evaluation of Bendectin in CD rats. Teratology 37:539-552, 1988.

3. Einarson TR, Leeder JS, and Koren G: A method for meta-analysis of epidemiological studies. Drug Intelligence and Clinical Pharmacy 22:813-824, 1988.

4. Biringer A: Antinauseants in pregnancy: teratogens or not? Canadian Family Physician 30:2123-2125, 1984.

PRODUCT MONOGRAPH (LABELLING) FOR DICLECTIN

Doxylamine succinate is an antihistaminic with anticholinergic and sedative properties. Antihistaminics are competing with histamine for the receptors of the effective cells. Pyridoxine HCl is a nutrient also called vitamin B_6

Toxicology: The oral LD50 of doxylamine is 470 mg/kg in the mouse and 250 mg/kg in the rabbit. The oral and sub-cutaneous LD50 of pyridoxine HCl are respectively 5500 and 3700 mg/kg in the rat.

For additional information on pregnancy and animal studies, see "PRECAUTIONS".

PRODUCT MONOGRAPH

DICLECTIN

An association of Doxylamine succinate -- Pyridoxine hydrochloride

Antinauseant
against nausea and vomiting
of pregnancy

Laboratorie Duchesnay
Laval, Quebec
(514) 668-9750
820014

DATE OF PREPARATION:
October 25, 1983

Action: The action of Diclectin is due to two unrelated compounds. Doxylamine succinate, an antihistaminic, provides the antinauseant and antiemetic activity; pyridoxine HCl provides a supplement of vitamin B_6 to prevent a possible pyridoxine deficiency during pregnancy. Also, studies have shown that pyridoxine could have an antinauseant activity. The antiemetic activity of Diclectin is delayed by a special coating of the tablet, a dose taken at night will be effective in the morning, the time mostly needed.

Indications: Diclectin is indicated only in cases of nausea and vomiting which are not relieved by traditional approaches (ingestion of salted biscuits or hot or cold liquids), and only when the symptoms interfere with normal alimentation or daily activities and are of sufficient severity to require medication (See Precautions-pregnancy).

PRECAUTIONS: **Pregnancy**

a) Animal studies

Teratogenecity studies of Diclectin or of its two active ingredients (doxylamine succinate and pyridoxine HCl) were done in different animal species: Sprague-Dawley rats, New-Zeland or Holland rabbits, NMRI mice, rhesus monkeys (*M. mulatta)* and cynomolgus (*M. fascicularis)*. The studies did not show any teratogenic effects due to Diclectin or to its active ingredients. However, two uncompleted recent studies could show a potential teratogenecity of Diclectin in certain species as indicated in the following paragraphs.

Studies in Sprague-Dawley rats and New-Zeland rabbits, at doses of Diclectin 90 times the maximal human dose (MHD) did not reveal any drug-induced fetal abnormalities. In a small scale study, pregnant cynomolgus monkeys were given Diclectin (10 to 20 times the MHD) by organogenesis. Abnormalities of the cardiac intraventricular wall were observed in 4 out of 6 foetus extracted at 100 days of gestation (normal gestation period is 160 days). A 40-days aborted foetus seemed normally developed. Three other foetus at term, did not show any cardiovascular abnormalities after usual clinical examinations at birth. In some other studies where rhesus and cynomolgus monkeys were administered Diclectin for a shorter period, the foetus were normal at birth.

Doxylamine succinate given to Wistar rats and NMRI mice at doses up to 60 times the MHD and to Sprague-Dawley rats and Holland rabbits up to 125 times the MHD, did not produce congenital abnormalities. Female Wistar rats given doses 125 to 175 times the MHD had foetus with ondulated ribs (7 to 10%) and hiatal hernia (2 to 6%). A global increase in foetal resorption, from a zero to three times were also observed in most of the rodents receiving 125 or more times the MHD.

b) Epidemiological studies

Many epidemiological studies (control and cohort) were done to evaluate the teratogenecity potential of Diclectin. It is concluded from these studies that there is no association between the use of

Diclectin and the presence of congenital abnormalities. A few of these studies leave the impression that a relation exists between the use of Diclectin and a particular congenital abnormality, but the associated abnormality differs from one study to the other. These results are considered hypothetical and not conclusive for many reasons: one of them is because they are from multiple analysis of the same data (i.e. studies of many drugs and many possible abnormalities at the same time). Recent epidemiological studies seem to indicate a possible association between the drug (or the treated disease or one and the other) and a pyloric stenosis. But more importantly, a third study did not reveal any association with this pathology. In the two studies, the stenosis could have been produced by the nausea or vomiting or other factor not associated with the medication. Certain abnormalities were particularly studied in other epidemiological studies and their relation with the use of Diclectin were not confirmed. More studies are actually in progress to clarify the problem. The cohort studies were designed to detect a small increase (less than 2X) of the global rate of malformations but they were not sensitive enough to eliminate the multiplication by two of a particular malformation (ex. 1/1000 to 2/1000).

For this reason, Diclectin should be used to treat nausea and vomiting of pregnancy only for cases resisting to traditional, non medicated procedures. Doctors who have decided to use a medication to stop nausea and vomiting of pregnancy should know that more studies on the risk of congenital abnormalities were done with Diclectin than with any other antinauseant drugs (a bibliography on Diclectin is available, on request, to the practitioner). Due to a risk of drowsiness, Diclectin must be prescribed with caution to automobile drivers and machine operators. It must also be used with caution in combination with alcohol and other CNS depressing drugs or with epileptic patients.

Secondary effects: The secondary effects are those produce by the two ingredients. Doxylamine succinate may cause drowsiness, vertigo, nervousness, epigastric pain, headache, palpitation, diarrhea, disorientation, irritability, convulsions, urinary retention or insomnia. Pyridoxine is a vitamin that is

generally recognized as having no adverse effects.

Symptoms and treatment of overdose: Signs and symptoms of intoxication are restlessness, dryness of mouth, dilated pupils, sleepiness, vertigo, mental confusion and tachycardia. The treatment if needed is gastric lavage, emetics or activated charcoal and a symptomatic treatment.

Dosage: **Adults**: Two tablets at bedtime. In severe cases or when nausea occurs during the day, one additional tablet in the morning and another in midafternoon.

CONSUMERS INFORMATION
DICLECTIN

Summary: Diclectin is indicated to treat nausea and vomiting that could happen during the first weeks of pregnancy. You should take this medication only if these symptoms are interfering with your alimentation or your daily activities and if other treatments prescribed by your doctor are ineffective. Ingestion of salted biscuits or toasts or drinking of hot or cold liquids in the morning at waking are some of these treatments.

There is no method to prove that in rare cases, a substance absorbed by a pregnant woman will not cause a congenital abnormality. Consequently, no medication, including Diclectin, should be taken during pregnancy unless it is absolutely necessary.

Diclectin could cause drowsiness, so before you know its action on you, be cautious while driving a care or operating any machine.

More information on Diclectin are found in this insert. Read it and keep it for further reference.

Use of Diclectin: Nausea and vomiting at the beginning of pregnancy are frequent. They are not generally the signs of a disease and they fade away or disappear after a few weeks, without treatment. For women who can tolerate these symptoms,

the simpliest treatments are salted biscuits or toasts or drinking of hot or cold liquids in the morning at waking. If these measures are ineffective and if the symptoms are sufficiently severe to interfere with the ingestion of food or your daily activities, then medication is desirable.
Diclectin contains two pharmaceutical ingredients: an antihistaminic (doxylamine) and vitamin B_6.

How to use Diclectin: In general, nausea and vomiting of pregnancy occur in the morning. Take two tablets at bedtime so the medication could be effective in the morning. If this dose does not relieve the symptoms, you could take another tablet in midmorning or in midafternoon. Your doctor can modify the dosage based on the time of appearance and the severity of the symptoms. If you have violent nausea and vomiting and if Diclectin is ineffective, consult your doctor. If you forget to take a dose of Diclectin, take it as soon as you realized it. Take the other doses as indicated. Do not take two doses at the same time, unless duely prescribed by your doctor.

Pregnancy and congenital abnormalities: Out of one hundred newborns, two or three have a serious congenital abnormality. This risk can be increased if the mother takes certain drugs or other substances like alcohol during pregnancy. The risk of congenital abnormality is increased if the substance is taken during the first 8 to 12 weeks of pregnancy, the time period at which the main organs of the foetus are under development. It is impossible to prove that a drug or any other substance taken during pregnancy is without any risk or totally innocuous.

Many studies were done in women taking this medication during pregnancy. In most of these studies, it was not proven that Diclectin increases the risk of congenital abnormality. A few studies have shown an increased risk of abnormalities but as the same results were not obtained in other studies, we cannot conclude that the abnormalities were due to this medication. However, no study was done in a sufficient scale to eliminate the possibility of a very small increase of risk. AS IT IS NOT POSSIBLE TO PROVE THAT A MEDICATION TAKEN DURING PREGNANCY WILL NOT PRODUCE A

CONGENITAL ABNORMALITY IN RARE CASES DICLECTIN SHOULD BE TAKEN ONLY IN ABSOLUTE NECESSITY. Even if this booklet warns you on the use of Diclectin, of all the antinauseant and antivomiting drugs used during pregnancy, this drug was the most studied. There are no supporting data to prove that another drug is safer to treat nausea and vomiting of pregnancy.

Nursing mothers should know that a small quantity of drug could be ingested by the infant. We do not know if undesirable effects could be produced on the baby.

General precautions: Diclectin could cause drowsiness. As long as you do not know how you are reacting to the medication, be cautious while driving a car or operating a machine. Deeper drowsiness could be produced if Diclectin is taken in combination with alcohol or other drugs like drugs for cough or colds, antidepressives, analgesics or tranquillizers.

If you had a severe reaction to an antihistaminic or to Diclectin in the past, advise your doctor. These reactions are severe drowsiness, insomnia, hyperactivity or excitation.

Secondary effects: In addition to drowsiness, Diclectin can produce vertigo, headache, confusion, irritability, insomnia, gastric pain. If you experience some of these effects or any other effect, consult your doctor.

Other information: For Diclectin to be effective, it must be taken as recommended on the label. This drug is specifically prescribed for you and your actual state of health. Do not give it to others even if they have the same symptoms. Even for you, do not use it for any other condition than the one for which it was prescribed.

If you think that you or someone else has taken an overdose, immediately call the antipoison center, your doctor, your pharmacist or the emergency service of the nearest hospital.
KEEP THIS DRUG AND ALL OTHER DRUGS OUT OF REACH OF CHILDREN.

If you want more information on Diclectin, consult your doctor or your pharmacist. They have available a more technical document (product monograph) that you could read.

Presentation: Each white, coated, delayed release tablet contains doxylamine succinate USP 10 mg pyridoxine HCl USP 10 mg. Bottles of 100, 500 and 1000 tablets.

Chemistry and pharmacology: The chemical name of doxylamine succinate is N, N-dimethyl-2-1-phenyl-1 (2-pyrimidyl) ethoxy-butanedioate (1:1). 2-a-2(dimethylamino) ethoxy-a-methylbenzyl pyridine (1-1 ethamine succinate. It is very soluble in water and alcohol, easily soluble in chloroform and slightly soluble in ether and benzene. Its formula is the following:

[FIGURE OMITTED]

The chemical name of pyridoxine HC1 is 5-hydroxy-6-methyl-3, 4 pyridine dimethanol HC1 or pyridoxile hydrochloride. It is easily soluble in water, slightly soluble in alcohol and insoluble in ether. Its formula is the following:

[FIGURE OMITTED]

14. District Court's Memorandum Decision and Order granting summary judgment to Merrell Dow, filed Nov. 1, 1989

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT
OF CALIFORNIA

WILLIAM DAUBERT, et al., *Plaintiffs*,	)	
v.	)	
MERRELL DOW PHARMACEUTICALS, INC., et al., *Defendants*.	)	CIVIL NOS. 84-2013-G(IEG), 84-2929-G(IEG) (Consolidated)
MICHAEL SCHULLER et al., *Plaintiffs*,	)	
v.	)	
MERRELL DOW PHARMACEUTICALS, INC., et al., *Defendants*.	)	

MEMORANDUM DECISION AND ORDER

EARL B. GILLIAM, UNITED STATES DISTRICT JUDGE:

The defendant's motion for summary judgment was scheduled for hearing on October 6, 1989, in Courtroom 7 before the Honorable Earl B. Gilliam. Plaintiffs were represented by Mary Gillick and Barry Nace. George Berry, Robert Dickson and Pamela Yates appeared on behalf of defendant. Having considered the points and authorities and oral argument of counsel, the court issues this memorandum decision and order granting defendant's motion for summary judgment.

FACTS

This case involves personal injuries sustained by plaintiffs. Infant plaintiffs and their guardians ad litem seek damages from defendant for injuries (limb reduction birth defects) allegedly sustained as a result of the mothers' ingestion of Bendectin during pregnancy. Bendectin is a prescription pharmaceutical product previously manufactured by Merrell Dow, indicated solely for the treatment of nausea and vomiting during pregnancy. Defendant has moved for summary judgment, arguing that plaintiffs have failed to sustain their burden of establishing a genuine issue of material fact regarding causation.

DISCUSSION

Summary judgment is proper "after adequate time for discovery and upon motion, against a party who fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial. . . ." *Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986). "[T]h[e] standard [for granting summary judgment] mirrors the standard for a directed verdict under Federal Rule of Civil Procedure 50(a). . . ." *Id.* at 323 (citing *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 250 (1986)).

In this case the defendant has moved for summary judgment. Plaintiffs, who have the burden of proof by a preponderance of the evidence, oppose the motion. The court must therefore determine "whether a fair-minded jury could return a verdict for the plaintiff [based] on the evidence presented." *Anderson v. Liberty Lobby, Inc.* 477 U.S. at 251-252. The court must view the evidence in a light most favorable to plaintiff, however, "[t]he evidence is insufficient if the strongest inference to be drawn in the plaintiff's favor is that defendant's negligence could *possibly* have been the cause of the accident." *Bieghler v. Kleppe*, 633 F.2d 531, 533 (9th Cir. 1980) (emphasis in original) (citing *Neely v. St. Paul Fire & Marine Insurance Co.*, 584 F.2d 341, 345 (9th Cir. 1978)). The plaintiff must show that defendant's negligence "was more probably than not the proximate cause of the accident" to defeat summary judgment and take the

issue to a jury. *Bieghler* at 533. The court should exclude inadmissible evidence objected to by either party prior to ruling upon the motion. *See, Hollingsworth Solderless Terminal Co., v. Turley* 622 F.2d 1324, 1335 (9th Cir. 1980).

Federal Rule of Evidence (FRE) 703, restricts the admissibility of scientific evidence. "A necessary predicate to the admission of scientific evidence is that the principle upon which it is based 'must be sufficiently established to have general acceptance in the field to which it belongs.'" *United States v. Kilgus*, 571 F.2d 508, 510 (9th Cir. 1978). Therefore, expert opinion not based on facts or data "of a type reasonably relied upon by experts in the particular field" is not helpful, but instead is confusing or misleading and should therefore be excluded. *See*, Fed.R.Evid. 403. *See also Barrel of Fun, Inc. v. State Farm Fire and Casualty Co.*, 739 F.2d 1028, 1033 (5th Cir. 1984) (excluding expert's opinion based on polygraph test). "Whether an expert's opinion has an adequate basis, and whether without it an evidentiary burden has been met, are matters of law for the court to decide." *Richardson v. Richardson-Merrell*, 857 F.2d 823, 829 (D.C.Cir. 1988), *cert. denied*, 107 L.Ed. 2d 171 (1989).

There are two schools of thought governing expert testimony in these Bendectin cases, and one seems to be prevailing in the federal courts. Unfortunately for the plaintiffs, the prevailing school of thought warrants summary judgment in this case.

The prevailing school is best exemplified by *Brock v. Merrell Dow Pharmaceuticals*, 874 F.2d 307 (5th Cir. 1989), *modified*, 884 F.2d 166 (5th Cir. 1989), *rehr'g denied, en banc*, 884 F.2d 167 (5th Cir. 1989) where the court held the following:

> We find, in this case, the Brocks' failure to present statistically significant epidemiological proof that Bendectin causes limb reduction defects to be fatal to their case.

Id. at 313. The court also noted:

> Hopefully, our decision will have the effect of encouraging district judges faced with medical and epidemiological proof

> in subsequent toxic tort cases to be especially vigilant in scrutinizing the basis, reasoning, and statistical significance of studies presented by both sides. However, we do not wish this case to stand as a bar to future Bendectin cases in the event that new and statistically significant studies emerge which would give a jury a firmer basis on which to determine the issue of causation.

Id. at 315. Several other cases are in accord with this reasoning. *See, Richardson v. Richardson-Merrell, supra*; *Lynch v. Merrell-National Laboratories*, 830 F.2d 1190 (1st Cir. 1987); *Hull v. Merrell Dow Pharmaceuticals, Inc.*, 700 F.Supp. 28 (S.D.Fla. 1988); *In Re Richardson-Merrell, Inc. "Bendectin" Products Liability Litigation*, 624 F.Supp. 1212 (S.D.Ohio 1985), *aff'd*, 857 F.2d 290 (6th Cir. 1988), *cert. denied* 109 S.Ct. 788 (1989); *Thompson v. Merrell Dow Pharmaceuticals, Inc.*, 229 N.J.Super. 230, 551 A.2d 177 (1988).

In medical cases like this one, courts must "critically evaluate the reasoning process by which the experts connect data to their conclusions in order for courts to consistently and rationally resolve the disputes before them." *Brock*, 874 F.2d at 310. Absent a scientific understanding of the cause of the birth defects at issue in Bendectin cases, causation may be shown only through reliance upon epidemiological evidence. *See, Richardson v. Richardson-Merrell*; *Lynch v. Merrell-National Laboratories*. *See also In Re Agent Orange Product Liability Lit.*, 611 F.Supp. 1223 (E.D.N.Y. 1985), *aff'd*, 818 F.2d 187 (2nd Cir. 1987) (stating that epidemiological studies were "the only useful studies having any bearing on causation" in Agent Orange cases).

In *Richardson*, Dr. Done, the plaintiff's expert, relied upon 1) chemical structure activity analysis, 2) *in vitro* (test tube) studies, 3) *in vivo* (animal teratology) studies, and 4) reanalysis of epidemiology studies. He used the results of these four types of studies to conclude that within a reasonable degree of certainty, Bendectin causes birth defects. The court concluded that Dr. Done's testimony lacked an adequate scientific basis:

> These three types of studies -- chemical, *in vitro*, and *in vivo* -- cannot furnish a sufficient foundation for a conclusion that Bendectin caused the birth defects at issue in this case. Studies of this kind singly or in combination are not capable of proving causation in human beings in the face of the overwhelming body of contradictory epidemiological evidence.

Richardson, 857 F.2d at 830. The court also rejected the reanalysis of the epidemiological studies:

> Dr. Done further admitted that no one who had published work on Bendectin had concluded that there was a statistically significant association between Bendectin and limb reduction defects. . . . Only by recalculating the data was Dr. Done able to obtain what he deems a statistically significant result. Moreover, the studies rejected by Dr. Done had been published in peer-reviewed scientific journals, while Dr. Done has neither published his recalculations nor offered them for review.

Id. at 831 (emphasis added).

The plaintiffs rely on *Oxendine v. Merrell Dow Pharmaceuticals, Inc.*, 506 A.2d 1100 (D.C.App. 1986) and other cases which basically give more deference to the expert's opinion. *Oxendine* is the leading Bendectin case in this regard, and the appellate court found that Dr. Done had a sufficient foundation for his testimony when he relied upon chemical analyses, animal studies, *in vitro* studies and recalculations of epidemiological studies:

> Dr. Alan Done, appellant's sole causation witness, had testified that no conclusion about Bendectin's effect on humans could be drawn from any of the four types of scientific data upon which he principally relied when each type was considered separately from the others. The [trial] court focused on this fact and concluded that if each type of data, viewed in isolation, was not sufficient to prove that Bendectin caused birth defects, then all of them taken

> together could not prove it either. In so doing, the trial court erred [by granting defendant's motion for J.N.O.V.].

Oxendine, 506 A.2d at 1104. The *Oxendine* court viewed the recalculations of epidemiological studies and the varying conclusions as involving a "classic battle of the experts." *Id.* at 1110. The court refused to find that plaintiffs had provided insufficient evidence to support the jury verdict solely because they had not provided a single original or recalculated epidemiological study which showed a statistically significant association between Bendectin and birth defects. *Id.* at 1107-10.

Oxendine is definitely in the minority camp. Although there appears to be no Ninth Circuit authority directly applicable to these Bendectin cases, this court must view the authority developed by three other federal circuit courts in *Brock*, *Lynch* and *Richardson* as highly persuasive.

In this case, the plaintiffs offer the opinion testimony of eight experts to establish that Bendectin is a teratogen (it causes limb reduction defects generally), and that Bendectin ingested by the mothers during pregnancy caused the limb reduction defects suffered by the infant Daubert and Schuller plaintiffs. Those experts are Dr. Adrian Gross, Dr. Stuart Newman, Dr. Alan K. Done, Dr. Shanna Swan, Dr. Jay Glasser, Dr. Wayne Snodgrass, Dr. Johannes Thiersch and Dr. John Palmer. Plaintiffs have submitted this testimony in the form of affidavits, deposition transcripts, and transcripts from previous trials.

Dr. Adrian Gross is a licensed and accredited veterinarian with experience in pathology and toxicology. *Ealy v. Richardson-Merrell* transcript, Exhibit 26 at pages 650-60. Dr. Gross would testify at trial that to within a reasonable degree of certainty Bendectin is a teratogen. Dr. Gross would base his opinion on animal studies which allegedly show a statistically significant association between Bendectin and doxylamine succinate (a component of Bendectin) and birth defects. *Id.* at pages 834-38.

Dr. Stuart Newman is a specialist in developmental biology. *Ealy* transcript, Exhibit 21 at pages 198-203; *Newman Affidavit* at pages 1-6. Dr. Newman would testify at trial that to within a reasonable degree of certainty "Bendectin is capable of interfering with the development of the limb in the human being and causing birth defects in the developing limb of the human being and that Bendectin is a human teratogen in the normal therapeutic dose." *Newman Affidavit* at page 9. Dr. Newman would base his opinion on *in vitro* studies and the pharmacology aspects of Bendectin. *Id.*

Dr. Alan Done is a medical doctor with specialties in pediatrics, clinical pharmacology and toxicology. *Oxendine v. Richard-Merrell* transcript, Exhibit 31 at page 3. Dr. Done's profferred testimony is unclear from the materials presented, but he apparently would testify that to a reasonable degree of certainty Bendectin is a teratogen. *Id.* at 854. Dr. Done apparently would base his opinion on analyses of the chemical structure and properties of doxylamine succinate animal studies *in vivo, in vitro* studies, and various informal and formal human studies, including epidemiological ones. *Id.* at 853.

Dr. Shanna Swan is an epidemiologist and biostatistician practicing in the field of reproductive epidemiology. *Ealy* transcript, Exhibit 12 at pages 3523-27. Dr. Swan would testify that to a reasonable degree of certainty, it is her opinion "that considering all available data that is provided in animal, *in vitro* and epidemiological studies, including the relative risks, the confidence limits and also the power of the studies, that it is more likely than not that Bendectin is, in fact, associated with limb reduction defects." *Swan Affidavit* at page 7. Dr. Swan would base her opinion on "the methodology that is generally and reasonably relied upon by epidemiologists to analyze, study and interpret data that has been collected, published and unpublished in trying to draw opinions concerning whether or not there is a cause and effect relationship between a drug and a birth defect." *Id.* at page 7-8.

Dr. Jay Glasser is a specialist in biostatistics, epidemiology and biometry. *Hill v. Merrell Dow* transcript, Exhibit 32 at pages 4-7; *Glasser Affidavit* at pages 1-4. Dr. Glasser would testify that "Bendectin is within a reasonable degree of epidemiological certainty associated with congenital disorders, including limb defects." *Glasser Affidavit* at page 7. Dr. Glasser would base his opinion on techniques that are generally and reasonably relied upon by biometrists, epidemiologists and biostatisticians. *Id.*

Dr. Wayne Snodgrass is an associate professor of pediatrics and pharmacology and toxicology. *Rudell v. Merrell Dow* transcript, Exhibit 20 at page 2. Dr. Snodgrass would testify that in his opinion Bendectin is a human teratogen. *Id.* at page 4. Dr. Snodgrass would base his opinion on results of various studies in several disciplines including pharmacology, toxicology, *in vitro* studies, animal studies and human studies. *Id.*

Dr. Johannes Thiersch is a specialist in pathology and pharmacology. *Thiersch Curriculum Vitae*, Exhibit 18. Dr. Thiersch would testify that the chemical composition and physiological activity of a drug are of great interest and importance in determining whether a drug is a teratogen. *Ealy v. Richardson-Merrell* transcript, Exhibit 22 at page 1596.

Dr. John Palmer is a professor of pharmacology. *Palmer Affidavit* at pages 1-4. Dr. Palmer would testify that in his opinion to a reasonable medical and scientific certainty Bendectin is a teratogen. *Id.* at page 7. Dr. Palmer would base his opinion on the pharmacological data, animal studies data, *in vitro* studies data, epidemiological data and other human data. *Id.* at pages 5-7. Dr. Palmer would also testify that he has examined the medical records of the plaintiff children and to a reasonable degree of medical certainty Bendectin was taken at a period of time such as to effect their development and it indeed caused their limb defects. *Id.* at pages 7-8.

The federal courts have held that epidemiological studies are the most reliable evidence of causation in this area. Accordingly, expert opinion which is not based on epidemiological evidence is not admissible to establish causation because it lacks the sufficient foundation necessary under FRE 703. *See, Brock*, 874 F.2d at 311-15; *Richardson*, 857 F.2d at 829-32; *Lynch*, 830 F.2d at 1194. Therefore, expert testimony concluding that Bendectin causes limb reduction defects which is based upon *in vitro* generally studies, chemical structure analyses and animal studies is insufficient to take the issue to the jury. The plaintiffs' experts must be competent to testify that some epidemiological study or recalculation shows a statistically significant relationship between the ingestion of Bendectin and birth defects and that this study forms the basis of their opinion. *Id.* In this case, the plaintiffs have failed to live up to the *Brock* mandate to provide some epidemiological evidence to support their claim that Bendectin is a teratogen. *Brock*, 874 F.2d at 315.

The defendants have introduced evidence that no epidemiological study ever performed has concluded that the use of Bendectin by pregnant women has a statistically significant association to birth defects in those women's children. *Report on the Safety of Bendectin/Diclectin for Use in the Management of Nausea and Vomiting of Pregnancy*, Exhibit J, Defendant's Reply to Affidavits of Plaintiff's Experts Submitted in Opposition to Defendant's Motion for Summary Judgment, at page 2 ("Controlled studies involving over 130,000 patients have not demonstrated any reproducible or consistent association of birth defects with Bendectin exposure. In fact, the results of the epidemiological studies are just what one might expect of an agent without reproductive or teratogenic risks."). *See also Statement of Steven H. Lamm*, Exhibit A, Defendant's Memorandum of Points and Authorities in Support of its Motion for Summary Judgment on the Issue of Causation at page 1 (after reviewing the world's literature on Bendectin and human birth defects, the studies "showed no difference in the risk of birth defects between those infants whose mothers had taken Bendectin during the first trimester of pregnancy and those infants whose mothers had not"). The plaintiffs' experts agree that none of the *published* studies show a statistically significant association between the use of Bendectin and birth defects. *See, e.g., Hill v. Merrell Dow Deposition of Jay H. Glasser*, Exhibit J, Defendant's Memoran-

dum of Points and Authorities in Support of its Motion for Summary Judgment on the Issue of Causation at page 164.

The plaintiffs argue that the absence of statistically significant epidemiological studies does not disprove the fact that Bendectin causes limb reduction defects. *See, e.g.*, Plaintiffs' Opposition to Defendant's Motion for Summary Judgment at 20-27; *Affidavit of Shanna Helen Swan* at pages 4-6. However, this argument directly contradicts the holdings of *Brock, Richardson* and *Lynch*. *See, supra*. The plaintiffs have the burden of proof, and they must come forward with statistically significant epidemiological evidence. The plaintiffs claim that Dr. Gross performed a new epidemiological study on Bendectin, but this is false. He simply recalculated a previously published study and tried to show that there actually was a significant relation between Bendectin and birth defects. *Letter to Thomas H. Bleakley*, Exhibit 40. Dr. Gross' "study" was apparently never published or subjected to peer review, and nowhere does it state that Bendectin sales increased the relative risk of limb reduction defects to a level significantly above 1.0 with a confidence interval that did not include unity. Dr. Gross alleges that this "study" shows "a statistically significant association that is highly significant" (Affidavit at page 11), but his allegation and this evidence is insufficient to take this matter to a jury. *See, Brock*, 874 F.2d at 312-13. Similarly, Dr. Swan's unsupported allegation that the Jick data "statistically significantly associates Bendectin and limb defects" (Affidavit at page 7) is similarly insufficient.

The court feels that the strongest inference to be drawn for plaintiffs based on the epidemiological evidence is that Bendectin could *possibly* have caused plaintiffs' injuries, therefore summary judgment is proper against them. *See, Bieghler v. Kleppe, supra*, 633 F.2d at 533. The court finds that there are no genuine issues of material fact with respect to causation and finds for the defendant on all causes of action.

IT IS SO ORDERED.

Dated: November 1, 1989

15. Court of Appeals' decision affirming the District Court, filed Dec. 20, 1991

UNITED STATES COURT OF APPEALS
For the Ninth Circuit

No. 90-55397

WILLIAM DAUBERT; JOYCE DAUBERT, individually and as Guardians Ad Litem for JASON DAUBERT, a minor; ANITA DE YOUNG, individually, and As Guardian Ad Litem for ERIC SCHULLER,

Plaintiffs-Appellants,

v.

MERRELL DOW PHARMACEUTICALS, INC., a Delaware corporation,

Defendants-Appellee.

Appeal from the United States District Court
For the Western District of Texas

(December 20, 1991)

Before: Alex Kozinski and Diarmuid F. O'Scannlain, Circuit Judges, and Stephen M. McNamee,* District Judge.

KOZINSKI, Circuit Judge:

Plaintiffs Jason Daubert and Eric Schuller suffer from limb reduction birth defects. They allege that these defects resulted

* The Honorable Stephen M. McNamee, United States District Judge for the District of Arizona, sitting by designation.

from the fact that their mothers used Bendectin, a prescription anti-nausea drug, during pregnancy. The plaintiffs seek damages from the drug's manufacturer, defendant Merrell Dow Pharmaceuticals.

Plaintiffs' evidence of causation consisted primarily of expert opinion based on *in vitro* and *in vivo* animal tests, chemical structure analyses and the reanalysis of epidemiological studies. Among the contrary evidence proffered by Merrell Dow was the affidavit of a physician and epidemiologist who reviewed all of the available literature on the subject, which included more than 30 published studies involving over 130,000 patients, and concluded that no published epidemiological study had demonstrated a statistically significant association between Bendectin and birth defects. Plaintiffs do not challenge this summary of the published record.

The district court determined that plaintiffs could not meet their burden of proving that Bendectin caused Jason's and Eric's birth defects and granted Merrell Dow's motion for summary judgment. *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 727 F. Supp. 570 (S.D. Cal. 1989).

A. Expert opinion based on a scientific technique "is admissible if it is generally accepted as a reliable technique among the scientific community." *United States v. Solomon*, 753 F.2d 1522, 1526 (9th Cir. 1985) (citing *Frye v. United States*, 293 F. 1013, 1014 (D.C. Cir. 1923)). We impose this requirement because such evidence "creates a substantial danger of undue prejudice or of confusing the issues or of misleading the jury . . . because of its aura of special reliability and trustworthiness." *United States v. Amarel*, 488 F.2d 1148, 1152 (9th Cir. 1973); *see also* Learned Hand, *Historical and Practical Considerations Regarding Expert Testimony*, 15 HARV.L.REV. 40, 50-52 (1901). Moreover, whether expert opinion can satisfy this requirement is reviewed *de novo* by an appellate court, for "the answer to the question about the reliability of a scientific technique or process does not vary according to the circumstances of each case. It is therefore inappropriate to view this threshold question of reliability as a matter within each trial

judge's individual discretion." *Reed v. State*, 391 A.2d 364, 367 (Md. 1978); *see also United States v. Williams*, 583 F.2d 1194, 1197-1201 (2d Cir. 1978) (applying *de novo* review to the question of the general acceptance of a scientific technique), *cert. denied*, 439 U.S. 1117 (1979).

For expert opinion based on a given scientific methodology to be admissible, the methodology cannot diverge significantly from the procedures accepted by recognized authorities in the field. If it does so diverge, it cannot be shown to be "generally accepted as a reliable technique," *Solomon*, 753 F.2d at 1526, and a district court must exclude it. If such evidence is admitted and materially affects the verdict, a judgment supported by this evidence cannot stand. *See Lindsey v. United States*, 237 F.2d 893, 897-98 (9th Cir. 1956).

B. Whether Bendectin is responsible for limb reduction defects is not a new question in the federal courts. Four of our sister circuits have considered whether plaintiffs could establish such responsibility in the absence of critically analyzed epidemiological studies establishing a connection between the use of the drug and the birth defects. *DeLuca v. Merrell Dow Pharmaceuticals, Inc.*, 911 F.2d 941 (3d Cir. 1990); *Brock v. Merrell Dow Pharmaceuticals, Inc.*, 874 F.2d 307, *modified*, 884 F.2d 166 (5th Cir. 1989), *cert. denied*, 110 S. Ct. 1511 (1990); *Richardson v. Richardson-Merrell, Inc.*, 857 F.2d 823 (D.C. Cir. 1988), *cert. denied*, 110 S. Ct. 218 (1989); *Lynch v. Merrell-National Labs.*, 830 F.2d 1190 (1st Cir. 1987) (opinion by Noonan, J., sitting by designation). Three circuits have concluded that the plaintiffs could not establish such a link. Considering largely the same evidence presented to the district court below, these courts held that the animal and chemical studies were insufficient to establish a link between Bendectin and birth defects, *Brock*, 874 F.2d at 313-15; *Richardson*, 857 F.2d at 830; *Lynch*, 830 F.2d at 1194, in part because the plaintiffs' own experts acknowledged the need to verify such data with epidemiological evidence.

Brock, 874 F.2d at 314; *Richardson*, 857 F.2d at 830.[1] These courts were unwilling to allow plaintiffs to rely on reanalyses of epidemiological studies because these reanalyses had neither been published nor subjected to the rigors of peer review. They found the methodology particularly problematic in light of the massive weight of the original published studies supporting the defendant's position, all of which had undergone full scrutiny from the scientific community. *See Brock*, 874 F.2d at 312-13; *Richardson*, 857 F.2d at 831; *Lynch*, 830 F.2d at 1193-96; *see also Christophersen v. Allied-Signal Corp.*, 939 F.2d 1106, 1111 n.8 (5th Cir. 1991) (en banc).[2]

Plaintiffs argue that reanalysis is a generally accepted scientific technique, so it follows that their experts were basing their opinions on a permissible methodology. But the reanalysis of epidemiological studies is generally accepted by the scientific community only when it is subjected to verification and scrutiny by others in the field. *See* Dore, *A Commentary on the Use of Epidemiological Evidence in Demonstrating Cause-in-Fact*, 7 HARV.ENV'L L.REV. 429, 438-39 (1983) (discussing requirements for original epidemiological studies). Plaintiffs' reanalyses

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[1] *Richardson* and *Lynch* held that expert testimony that Bendectin caused birth defects, based solely on animal and chemical tests and reanalyses of epidemiological studies, was inadmissible under Federal Rule of Evidence 703, and that therefore plaintiffs had failed to present evidence to support a jury verdict in their favor. 857 F.2d at 830-831; 830 F.2d at 1193-96. *Brock* did not hold that the plaintiffs' expert testimony was inadmissible, but did decide that it was insufficient to support the jury's verdict. 874 F.2d at 315.

[2] The Third Circuit has left open the possibility that expert testimony based on the reanalysis of epidemiological studies may be admissible if it can be shown to be reliable and not too likely to overwhelm, confuse or mislead the jury. *See DeLuca*, 911 F.2d at 955 (remanding case for district court to reconsider the admissibility of plaintiffs' expert testimony). Because the Third Circuit has specifically rejected the *Frye/Solomon* "generally accepted" standard, *United States v. Downing*, 753 F.2d 1224, 1236-37 (3d Cir. 1985), we find the court's analysis in *DeLuca* to be contrary to our established precedent and decline to follow it.

do not comply with this standard; they were unpublished, not subjected to the normal peer review process, and generated solely for use in litigation.[3] It does not suffice that the expert's methodology meet *some* of the requirements imposed by the scientific community; it must meet *all* of the essential requirements. Selective borrowing from generally accepted scientific methodology does not satisfy *Solomon*'s rigorous standard.

C. *Lynch*, *Richardson* and *Brock* reflect a well-founded skepticism of the scientific value of the reanalysis methodology employed by plaintiffs' experts; they recognize that "the best test of certainty we have is good science - the science of publication, replication, and verification, the science of consensus and peer review." P. Huber, *Galileo's Revenge: Junk Science in the Courthouse*, 228 (1991). For the convincing reasons articulated by our sister circuits, we agree with the district court that the available animal and chemical studies, together with plaintiffs' expert reanalysis of epidemiological studies, provide insufficient foundation to allow admission of expert testimony to the effect that Bendectin caused plaintiffs' injuries. Accordingly, plaintiffs could not satisfy their burden of proving causation at trial. *See Christophersen*, 939 F.2d at 1109 ("When the contested evidence is essential to the cause of action and the trial court has excluded the evidence, we may decide the appeal . . . solely on the basis of the soundness of the evidentiary ruling. For if we uphold the exclusion of essential evidence, the [review of the summary judgment ruling] becomes academic.").

AFFIRMED.

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[3] Scientific studies conducted in anticipation of litigation must be scrutinized much more carefully than studies conducted in the normal course of scientific inquiry. This added dose of skepticism is warranted, in part, because studies generated especially for use in litigation are less likely to have been exposed to the normal peer review process, which is one of the hallmarks of reliable scientific investigation. *See Brock*, 874 F.2d at 313; *Richardson*, 857 F.2d at 831 n.55; *Perry v. United States*, 755 F.2d 888, 892 (11th Cir. 1985).

16. Denial of panel rehearing and rehearing en banc, filed Apr. 8, 1992

APPENDIX C

UNITED STATES COURT OF APPEALS
For the Ninth Circuit

No. 90-55397, D.C. No. CV-84-2013-G(I)

WILLIAM DAUBERT; JOYCE DAUBERT, individually and as Guardians Ad Litem for JASON DAUBERT, a minor; ANITA DE YOUNG, individually, and As Guardian Ad Litem for ERIC SCHULLER,

Plaintiffs-Appellants,

v.

MERRELL DOW PHARMACEUTICALS, INC., a Delaware corporation,

Defendant-Appellee.

(Filed April 8, 1992)

ORDER

Before: KOZINSKI and O'SCANNLAIN, Circuit Judges, and MCNAMEE,* District Judge.

The petition for rehearing is denied. The full court has been advised of the suggestion for rehearing en banc and no active judge has requested a vote. The suggestion for rehearing en banc is therefore rejected. Fed.R.App.P. 35(b).

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* The Honorable Stephen M. McNamee, United States District Judge for the District of Arizona, sitting by designation.